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13. ABSTRACT *(Maximum 200*

During year two of this project, the Cancer and Leukemia Group B (CALGB) entered 40 breast cancer patients into the Linked Registry according to procedures specified in CALGB Protocol 9484. The telephone interviews of patients have gone smoothly and the entry of data from the interviews by the CALGB Data Management Center has been free of problems. The flow of patient samples from CALGB 9484 has begun and the storage of samples and preparation of DNA has been problem-free. The number of institutions participating in the project has been limited by the actions of IRBs many of which have disapproved the protocol because of concerns about the risks of genetic testing. In view of this, the protocol has been amended in a manner that will reduce or eliminate concern about this issue and to improve the efficiency of patient entry. A Certificate of Confidentiality has been granted to this project further reducing the risk to patients contributing samples for studies of genomic DNA.

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Progress Report
Contract DAMD 17-94-J- 4114 from U.S. Army Research and Materiel Command

October 1, 1995-September 30, 1996

Prepared by O. Ross McIntrye, M.D. Principal Investigator

I. INTRODUCTION:

A. Nature of the problem:

The use of adjuvant chemotherapy following local treatment of the tumor has clearly benefited many patients with breast cancer[1]. On the other hand, adjuvant chemotherapy carries with it a number of potential risks including secondary malignancies. Thus, it would be desirable to give adjuvant therapy only to the subgroup of women with breast cancer who are most likely to have a recurrence. Although clinical findings are useful in assigning prognosis [2,3], these alone are imperfect measures and there is hope that additional tests, such as the detection of certain somatic mutations in the tumor, will prove helpful in guiding the decision as to who should and who should not receive adjuvant chemotherapy. These considerations have now been formalized in the language describing such testing and a distinction between prognostic factors (which forecast clinical outcome) and predictive factors (which predict response and influence selection of specific forms of therapy) has been offered.[4]

In addition to our ability to detect a number of somatic mutations that may predict the risk of recurrence, it is now possible to identify those individuals who carry the BRCA 1 or BRCA 2 gene in their germline[5,6,7,8,9,10]. It is anticipated that additional genes conferring an increased risk of breast cancer upon their carriers will be identified. The presence or absence of such genes in the germline may influence not only risk of occurrence but also the response to treatment and other outcomes in these patients. Knowledge that such genes are present may predict the likelihood of a second primary in women who have already been diagnosed with breast cancer, and may assist in guiding prevention efforts in other members of the family who carry the gene.

The investigators who are participating in this project will test a number of hypotheses that were described in our original application. Three additional proposals for use of the resources provided by this project were presented in the progress report for 1994-95. In 1996 one additional proposal has been received:

Because interactions of erb-2 and p53 with type of adjuvant therapy received have already been observed (see next section), it is important that assays of putative prognostic factors be performed on well-characterized groups of patients receiving adjuvant chemotherapy according to standardized protocols. The registry being created with support from this grant is quite different from usual population-based registry concepts. Instead, it may be viewed as a library in which clinical information

on groups of uniformly staged and treated patients is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It is possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[11]

In cohorts of patients treated on our protocols endpoints such as time to recurrence, site of first recurrence, percentage of planned adjuvant therapy received, and detailed initial staging information are available. Moreover, there is an opportunity to collect additional information from such patients that may be useful in predicting the likelihood of a germline mutation or other factors that may interact with treatment and prognosis.

The identification in a patient or family member of a breast cancer patient of a heritable gene conferring an increased risk of breast cancer carries with it economic and psychosocial risks[12] in addition to the possibility that the gene is not causally related to the cancer in that patient[13]. We will be able to assess the impact of determining genomic susceptibility on individuals *most in need* of this type of information. The creation of the linked registry supported by this grant offers the opportunity for the patients and those involved in the laboratory to be joined in the pursuit of new knowledge. It is important that this pursuit be conducted in a manner offering the least psychological stress and the greatest protection from adverse social and economic consequences to those who participate. Collection of detailed information at the time of entry to the study relating to this as well as other areas will allow hypotheses concerning this aspect of the study to be tested.

B. Background and Previous Work

In order to show the value of our linked-registry we offer the example that follows. We emphasize that this is an early example of the type of success we hope to achieve. The work that produced these results followed the successful integration of effort by a number of individuals, funded by a variety of sources including NCI grants to the CALGB, R01 and SPORE grants held by certain of the investigators, and by a small foundation grant to the CALGB.

Example: In 1989, the CALGB activated protocol 8869 with Hyman Muss, M.D., Bowman Gray School of Medicine, as study chair. The goal of this study was to pursue possible relationships between S phase and ploidy in breast cancer specimens, as determined by flow cytometry techniques, with clinical outcome in patients treated on our adjuvant protocol 8541. The protocol provided for collection of fixed tissue on a random sample of patients entered on the treatment study. As 8869 progressed, and as techniques were perfected for the immunohistochemical determination of erbB-2 and P53 on paraffin embedded specimens, the protocol was amended so that Ann Thor, M.D., of Massachusetts General Hospital, could apply these tests to the specimens. In addition, molecular assessment of these tissues by Edison Liu, M.D., of the University of North Carolina was added at that time.

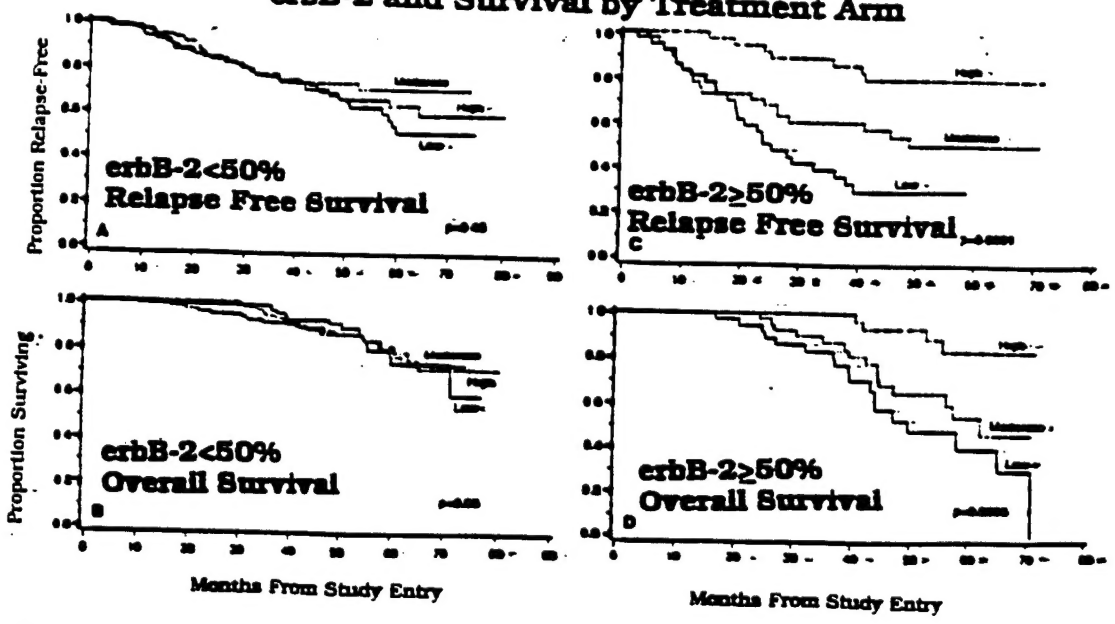
The treatment protocol, 8541, tested three CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) adjuvant regimens for which the dose schedule and dose intensity are shown in Table 1. Patients receiving the more dose intense regimens had significantly longer disease-free and overall survival than patients receiving the lower dose regimen.[14, 15]

Table 1
Dose and Dose-Rates

Arm	I	II	III
Dose Rate mg/M2/week			
Cyclophosphamide	150	100	75
Doxorubicin	15	10	7.5
5-Fluorouracil	300	200	150
Cumulative Dose mg/M2			
Cyclophosphamide	2400	2400	1200
Doxorubicin	240	240	120
5-Fluorouracil	4800	4800	2400

When these treatment results are combined with studies of S-phase, P53 and erbB-2, an unexpected highly significant finding emerged.[16,17] The effect was most dramatic for erbB-2 which is shown in Figure 1, although similar results occurred when P53 overexpression[18,19] or S-phase were analyzed.

Figure 1
erbB-2 and Survival by Treatment Arm



As shown, the patients whose tumors overexpressed erbB-2 had a significantly longer disease-free and overall survival than those whose tumors did not overexpress erbB-2. There was no significant difference in disease-free or overall

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survival with any of the three treatments for those patients whose tumors did not overexpress erbB-2. These findings indicate that the benefit of intensive adjuvant therapy with this combination is limited to a subgroup of patients. From the clinical data we know that the group receiving the more intensive treatments fared better, but without the integrated laboratory data, of course, we would have no indication that this intensive treatment group was comprised of two populations, one which did, and the other which did not, benefit from the more intensive treatments.

As stated above, 8869 originally collected specimens on a randomly selected sample of all patients on 8541. Committing almost all of the very limited non-NCI funds available to the CALGB, we immediately set about to collect all of the remaining blocks available from patients on this study. During the last year the analysis of tests for S phase, P53 and erbB-2 which were performed on this second set of specimens has been going forward and two publications are in the final stages of preparation. These publications will provide further evidence for or against the hypothesis that the doxorubicin dose intensity in the CAF regimen we used interacts with P53 and erbB-2 overexpression in the prediction of treatment outcome.

Conclusion from the Example: The issue of dose intensity, time to failure or death, and erbB-2 (or P53) overexpression would not have been raised if the laboratory study had not been conducted on tissue samples of similarly staged patients receiving randomly assigned, defined therapeutic regimens.

The rapidly building capabilities for this type of study and the excitement attending the initial success of combining laboratory and clinical information on our patients has led to several meetings of investigators. At these meetings there has been vigorous discussion of the opportunities for new projects as well as the need to develop new resources to serve CALGB as well as other investigators. The infrastructure category of the Army BAA offered an ideal mechanism to advance our studies and to assist other investigators in the field.

C. Purpose and Hypothesis:

We are using well-established methods within the CALGB and new procedures developed with support of this project to create a specialized registry which links molecular and epidemiological data with data from uniformly staged breast cancer patients receiving defined therapy. This registry of data, tumor tissue, and other specimens will enhance the research of 30 to 50 peer reviewed and funded investigators during the course of the project. It is intended that the level of quality control as well as the comprehensiveness of the registry will make it an unparalleled resource for investigators pursuing the relationship between tumor genetics, tumor biology and the prevention and treatment of breast cancer.

D. Methods of Approach - Specific Technical Objectives:

This project creates a linked-registry based upon the capabilities of CALGB to rapidly enroll large numbers of well-characterized incident breast cancer patients to its treatment trials. It takes advantage of a unique opportunity to link data on the

biology of breast cancer with information on uniformly staged patients who receive defined treatments. Since TNM staging defines rather broad categories[20], especially in stage II breast cancer, we anticipate that an exploration of the sources of heterogeneity with newly developed markers will advance our understanding of the disease.

This registry is used for studies on epidemiological and molecular characteristics that influence the outcome for breast cancer patients. Nested family studies that focus on factors related to etiology will also be possible if other support is achieved for this activity. The registry will provide information critical to the design of future chemo-prevention studies, the interaction of treatment with factors that govern disease progression and metastasis, and will be instrumental in guiding the design of future adjuvant treatment trials.

Specific technical objectives are as follows:

a. To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.

b. To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having 2 or more relatives with breast, ovarian, or colon cancer.

c. To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database. The study will obtain exposure information from affected and unaffected first-degree relatives of patients with a family history of cancer.

d. To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine from the same patients and family members.

e. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB data base and to prioritize use of this information.

g. To modify the CALGB data base and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.

h. To augment resources at CALGB institutions in order to procure the above described information and specimens.

II. BODY OF THE APPLICATION

A. Description of the Methods:

In contrast to laboratory-based investigations, the linked registry employs new and existing committees of the CALGB and new resources created by the registry to collect specimens as well as epidemiologic and psychosocial information. It provides a mechanism to integrate registry data with clinical information derived from CALGB clinical trials. Specimens and information from the registry are to be used by laboratory-based investigators, epidemiologists, and others to test various hypotheses bearing on breast cancer cause, risk, progression, response to treatment, as well as to determine the psychosocial impact of this testing.

This project is based at Dartmouth Medical School where Dr. McIntyre, the Principal Investigator, serves as the James Carroll Professor of Oncology, Emeritus. Subcontracts from Dartmouth provide support for activities at the University of North Carolina (DNA extraction and epidemiology), Georgetown University (Lombardi Cancer Center - serum and urine bank), Roswell Park Cancer Institute (tissue sectioning, tissue banking and pathology review), the University of Chicago (communication, protocol editing, and regulatory compliance) and Duke University (statistics and data management). Where possible, efficiencies are achieved by using methods of communication, data submission, protocol editing, meeting arrangements, etc., that have been developed for the CALGB.

The Principal Investigator, Dr. McIntyre, is assisted in the management of the project by three committees:

Table 2
Linked Registry Steering Committee

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Committee Chair	Dartmouth
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology Com. Chm	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Daniel Hayes, M.D.	Cor. Sci. Chm.	Georgetown Univ.
Larry Norton, M.D.	Br. Com. Chm	MSKCC
Lauren Schnaper, M.D.	Surgery	U. Maryland
Lynn Dressler, M.A.	Cor. Sci. Com.	U. North Carolina
Dale Sandler, Ph.D.	Epi. Com. Chm.	NIEHS
Debra Collyar	Patient Advocate	External Member
Susan Moore	Patient Advocate	External Member

This interdisciplinary committee is responsible for overseeing the conduct of the project, assisting with the integration of projects that will use the registry so as to insure the greatest productivity from it, and setting priorities for use of the resource.

Epidemiology Resource Committee: This committee is responsible for the design of the data collection instruments employed by the linked registry. It is also

responsible for the review and prioritization of projects requesting use of linked registry data. The committee is chaired by Dale Sandler, Ph.D, Chief, Environmental and Molecular Epidemiology Branch, NIEHS, and Chair of the CALGB Epidemiology Committee.

Table 3
Epidemiology Resource Committee

Name	CALGB position	Institution
Dale Sandler, Ph.D.	Chair	NIEHS
Robert Millikan, DVM, Ph.D.	Co P.I.	U. North Carolina
Beth Newman	Epidemiologist	U. North Carolina
Stephanie London MD, Ph.D.	Epidemiologist	Univ. So. Cal.
Matthew Longnecker, MD, ScD	Epidemiologist	UCLA
Thomas Sellers, Ph.D.	Epidemiologist	U. Minnesota
Fred Li, M.D.	Epidemiologist	Dana Farber
Donald Berry, Ph.D.	Statistician	Duke University
Virginia Ernster Ph.D.	Epidemiologist	U. of California S.F.
Lauren Schnaper, M.D.	Surgeon	U. of Maryland

In brief, the committee has developed and implemented procedures to collect family cancer history, reproductive and hormone use history, and other exposure information from all breast cancer patients enrolled in CALGB treatment trials. Tumor tissue and germ-line DNA is collected from breast cancer patients as described below.

Breast cancer patients who are registered to CALGB treatment trials are informed by CALGB clinical research associates and nurse oncologists about this project at those CALGB institutions where CALGB 9484 has been activated. Patients are offered the opportunity to participate in a treatment companion protocol, CALGB 9484 that provides for the gathering of epidemiological data and collection of specimens. During 1996 CALGB protocol 9484 was amended so as to improve patient accrual. The revised protocol has been reviewed and approved by the Army Research and Materiel Command. The amended protocol was issued to CALGB institutions on October 15, 1996. The rationale for the changes embodied in the amended protocol are given in section B, below. The methods described in this section are those specified in the amended protocol and differ somewhat from procedures described in last year's progress report.

Breast cancer patients who give their informed consent for treatment on selected CALGB breast cancer protocols are asked to return a self-completed questionnaire and to give permission for submission of their biopsy specimen as well as blood and urine samples. In addition we ask the patient's permission to conduct studies of germline DNA on cells obtained from a blood sample. The consent form for these procedures is integrated with that of the treatment protocol and administered at the same time. We follow all consent procedures mandated by Department of Defense regulations and IRBs at participating institutions. **The self-completed questionnaire is contained in the amended CALGB 9484 included in this report as Appendix 1.**

Questionnaires are collected by the institutional clinical research associates who submit them to the CALGB Data Management Center at Duke. There, they are examined for completeness, checked for errors, and the data entered in the CALGB data base.

On the basis of information from the self-completed questionnaire, the investigators at UNC, under the direction of Dr. Millikan, categorize the patients into three groups:

a. Patients with any first or second degree relative with breast or ovarian cancer.
b. Patients aged <50 years with no family history.
c. Patients aged ≥ 50 years with no family history.

All patients in groups a and b, and a random sample of group c, above are contacted by the telephone interviewer. Consenting patients are then queried in the telephone interview. **The questionnaire administered by telephone is furnished in Appendix 2.**

Our previous experience has shown that it is necessary to conduct telephone or in-person interviews to verify and complete family histories and exposure history. Because recall bias is introduced in self-reports of breast cancer occurrence in first degree relatives[21] a carefully administered interview to confirm the self-reporting is indicated. Telephone interviews work as well as in-person interviews for this purpose.[22,23]

We have found an 85% participation rate in our telephone interview inquiring about risk factors for leukemia and this is carried out while these acutely ill patients are hospitalized. While the response rate for the self-completed questionnaires is often lower than that for telephone or in-person interviews, we anticipate a high rate of return of the initial questionnaire because institutional data managers are responsible for retrieving the completed forms. We have used telephone interviews with great success not only in the environmental exposure studies in leukemia patients but also in the long-term follow-up of patients with successfully treated Hodgkin's disease.[24,25,26]

Tissue Resource Coordinating Committee: The Breast Tissue Coordinating Committee, Chaired by Lynn Dressler, University of North Carolina, serves to coordinate the systematic collection and archiving of breast tissue, germ-line DNA, serum, plasma, and urine.

Table 4
Tissue Resource Coordinating Committee

Name	CALGB position	Institution
Lynn Dressler M.A.	Chair	U. of North Carolina
Robert Millikan, DVM, Ph.D.	Co P.I.	U. of North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Joe Gray, Ph.D.	Genetics	U. of California S.F.
Daniel Hayes, M.D.	Oncology	Georgetown
Hyman Muss, M.D.	Oncology	University of Vermont
Donald Berry, Ph.D	Statistician	Duke University

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1. **Fixed tissue:**

When the patient signs an informed consent to participate in CALGB 9484 institutional data managers arrange for submission of tissue blocks by contacting the coordinating pathologist at a CALGB main member or affiliate institution. Paraffin blocks and sample submission forms are received at the CALGB Pathology Office directed by Dr. Maurice Barcos at Roswell Park Cancer Institute. There, they are logged into the CALGB data base and histologic sections are made. Four micron slides from these submissions are sent to Dr. Fred Koerner at the Massachusetts General Hospital who reviews them for accuracy of diagnosis, and delineates areas on the slides containing homogeneous malignant tissue. These slides are returned, the blocks trimmed, if necessary, to yield 4 FISH (immunohistochemistry) and 10 micron sections (PCR, FISH) of homogeneous tumor, as well as non-malignant breast tissue. At least 30 sections are removed: 20, 4 micron sections for immunohistochemistry/FISH/ISH assays and 10, 10 micron sections for molecular based assays requiring extracted DNA. At three levels, sections are taken and stained and examined to ensure representative tissues is being distributed for all assays (See Appendices 6 and 7). We ask for permission to retain the blocks for future sectioning and store them at 4° C. If this is not granted, we prepare sections as described above, as determined by the amount of tissue available in the block (See Appendix 6). Prior to the return of the blocks to the submitting institution we prepare additional sections.

2. **DNA procurement:**

Somatic DNA: From the specimens collected as described above, individual investigators prepare somatic DNA according to their established laboratory procedures.

Germline DNA: EDTA anticoagulated peripheral blood is collected and shipped to the UNC DNA extraction laboratory overnight for lymphocyte separation and DNA extraction. Lymphocyte DNA is prepared using the ABI DNA extractor and the DNA stored at -70°.

Quality control/quality assurance/sample distribution for DNA extraction:

The CALGB/RPCI Pathology tissue bank cuts and mounts a series of 10 micron sections on uncoated slides from each block according to their routine procedures. These procedures incorporate careful quality control and quality assurance parameters, including changing the microtome blade between each block to prevent contamination of DNA on the blade surface, cleaning the waterbath surface between each block, and wearing gloves to process blocks. As part of the routine processing procedure at the RPCI Pathology bank, sections for H & E staining are cut immediately preceding and after those cut for molecular (10 micron section) and immunohistochemical (4 micron) assays. The CALGB Pathology office reviews all H & E sections to ensure that representative and sufficient tumor tissue is present throughout all sections cut for assay. In addition, to enrich for tumor tissue, tumor rich versus tumor poor areas are marked on the corresponding H & E section(s). For DNA processing, the corresponding H & E section will be superimposed on the

unstained 10 micron sections and the circled region of tumor rich areas will be isolated and scraped into an Eppendorf tube by the technician in the UNC tissue bank. DNA lysates will be prepared as described below from each tumor tissue. DNA lysates are stored at 4 degrees centigrade for short term storage and at -85 degrees centigrade for long term banking. DNA lysates are stored in vials and multiple aliquots of processed DNA are prepared. As indicated above, DNA processing occurs in a clean area: a special room where only tissue and DNA processing is allowed to prevent DNA contamination, a major problem in PCR based studies. Distribution of samples is defined in the CALGB protocol and is rigorously monitored both in house and through the CALGB DMC Tissue tracking system. A protocol is only developed once the study has received appropriate review and approval from the Solid Tumor Correlative Science Committee and Central Tissue Bank Committee.

Protocol for DNA Extraction from Tissue Sections:

Formalin fixed paraffin embedded tissue sections (1-5 depending on cellularity and size of tumor area) are gently scraped from uncoated glass slides (uncoated slides facilitates the scraping process, although tissue can be scraped from coated slides as well) with a 200 ml micropipet tip into a 1.5 microfuge tube. In a fume hood, 500 ml of xylene is added to each tube and the tubes are thoroughly mixed. After a 5 minute centrifugation at 1200 rpm, the supernatant is discarded into a xylene waste container, and the pellet is extracted twice with 500 ml of autoclaved 95% ethanol. the pellets are dried for 2 hours or more in a vacuum dessicator before addition of 200 ml lysis buffer containing Proteinase K and overnight incubation at 58° C. On the following day the Proteinase K is inactivated by a 10 minute incubation at 95° C. Any remaining debris is removed by a 10 minute centrifugation in the microfuge, and the supernatant is ready to use as a template source for a variety of molecular analyses.

3. Collection of plasma, serum and urine:

Plasma samples are collected into EDTA-containing collection tubes. After separation from the cellular component, the plasma are aliquoted to a freezing tube, labeled, and frozen at -20°C at the participating institution. These samples are batched and when several tubes have been collected, they are shipped on dry ice overnight to Georgetown University (Lombardi Cancer Center), where they are catalogued, kept at 4°C for short term storage and -70°C for long term storage. Frozen urine is shipped in batches to the Georgetown for processing and analysis.

4. Training of data managers:

On a regular basis, not less than once a year, a portion of the CALGB Data Managers workshop is devoted to instruction of the proper methods of obtaining and shipping the above specimens.

5. **Receipt of Specimens:**

Centers receiving specimens will electronically report to the CALGB data base the receipt and condition of the specimen using standard CALGB procedures.

6. **Tracking of Patient Specimen Submission:**

The CALGB data management system tracks patients who are entered on CALGB protocols and plans to implement a system soon that will generate reminders to institutions that have entered patients on treatment protocols if the required specimens have not been received at the appropriate office or lab in a timely manner.

Use of the data from the Linked Registry: All uses for the information in the linked registry will be described in formal protocols that define the objectives, methodology, and statistical assumptions. These must be reviewed and approved by the Steering Committee. **Letters to the users setting out the agreement under which they use the registry are included in Appendix 3.** Written proposals from the scientific community are considered if they do not compete with approved projects already underway, and are prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we use the same scale that will be used for projects developed by CALGB members. In all cases emphasis is placed upon the level of innovation and the track-record of the investigator with respect to peer review and publications. We plan to deliberately include projects, however, from young investigators without a track record, if they are endorsed by knowledgeable mentors and are innovative.

The availability of the Linked Registry is publicized through usual channels of scientific communication. In addition, the CALGB newsletter that is sent to many investigators outside the CALGB will be used as will news releases to "The Cancer Letter", and similar publications. Eventually, information about the CALGB Linked Registry will be available at the CALGB World Wide Web site.

B. <u>Progress in Year 2.</u>

Introduction: The progress report for year one submitted one year ago mentioned that patient accrual to this study was less than anticipated. It also described steps that were being taken to address this problem. At that time, it appeared that the availability of genetic counseling within CALGB institutions, a resource needed if the results of testing for familial cancer gene testing were to be made available to study subjects, was the principal stumbling block to adoption of the protocol at many CALGB institutions. We recognized this need during the design phases of the project and described it in our application. Beginning in the second year of the project we instituted a program intended to provide extensive training in the necessary genetic counseling skills. As structured this program was to be completed during the interval prior to the period we anticipated that results from the project would be available for our patients (about year 4 of the project).

Despite the progress of the training program, the number of institutions approving the study remained far less than anticipated and it became clear that other aspects of the project were the cause of concern at our institutions. During this time, several articles appeared in the scientific and lay press calling attention to the potential risks involved in familial gene studies. Although these publications recommended that such testing should occur in the context of research trials of the sort this project represents, it became clear that Institutional Review Boards (IRBs) had a number of concerns about the conduct of familial cancer gene studies. We were asked to assist in providing information addressing these concerns and ultimately, as described below, decided to amend the protocol to address the principal issues these committees raised about the project.

Apart from accrual, all other goals set for year two of the project have been met. The pilot testing of the questionnaire has been completed, specimen submission has gone smoothly and a review of the forms submitted on patients entered to date has revealed no problems.

Patient Accrual and Revision of CALGB Protocol 9484 to Improve Accrual: Table 5 below shows accrual to the Linked Registry (CALGB Protocol 9484) and to concurrent CALGB breast cancer treatment trials.

Table 5
Accrual to CALGB 9484 vs Samples Received on Concurrent CALGB Treatment Studies (cut off date 9/16/96)

Registrations to CALGB 9484	40
Registrations to CALGB Treatment Protocols	994
Samples received on CALGB Treatment Protocols	779

Inspection of table 5 indicates that only a small fraction of patients placed upon concurrent treatment trials entered CALGB 9484. Tissue blocks have been received on 78% of those entering treatment trials and it should be noted that this is a minimal figure since there is a lag between patient registration on protocol and the actual receipt of tissue blocks in the CALGB Pathology Office. On the other hand participation in 9484 has been limited to those few institutions in which IRB approval of the protocol has occurred. It is also clear that the cumbersome process of obtaining two consents, one for treatment and the other for linked registry participation, has impaired patient registration in those institutions in which IRB approval has been granted. The submission of tissue blocks on a large fraction of patients placed upon treatment trials demonstrates that the linked registry concept is technically feasible if IRB approval of the protocol occurs at all CALGB institutions and if the paperwork required for patient entry to the protocol can be simplified at the institutional level

In March of 1996, after taking several steps to improve accrual, we prepared an amended protocol to correct the underlying causes of the poor accrual. These changes are currently under review by the Army Research and Materiel Command. It is anticipated that the revised project, as described more completely below, will allow achievement of the original goals.

Background for protocol amendment:

1. The original protocol held a requirement that institutions provide genetic counseling to patients who provided germline DNA for familial cancer gene studies. This policy was the outcome of a meeting with cancer advocates, experts in familial gene studies, CALGB investigators and federal regulators that examined the risks and benefits of providing the results of familial gene studies to patients who participated in this project. (See previous progress report for details).

In response to this, the CALGB held workshops on November 4, 1995 and May 3, 1996 (with a third workshop scheduled for November, 1996) which provided training in genetic counseling for institutional personnel. The agendas for these well-attended workshops are included as Appendices 4 and 5. Although the workshops were a component of a long-range program intended to expand the cadre of genetic counselors available for the purpose of advising breast cancer patients in participating institutions by the time the results from our studies became available, this did not result in the anticipated increase in the number of institutions approving the protocol for activation.

2. A large number of questions from IRBs at CALGB institutions were directed to us during this period. The responses to certain of these were provided to institutions in a lengthy Question and Answer document (included as appendix in last year's progress report) and which was received by institutions early in year two of the project.

3. By March, 1996, it was clear that our attempts to allay the concerns of institutional IRBs had not succeeded. For instance, in addition to the concerns raised in the question and answer format, above, there were others:

a. Institutions had not yet perfected internal record keeping procedures that ensured that familial gene studies would be held confidential from potential employers and health insurers. i.e. a number of IRBs took no issue with the research project but noted that their institutions lacked an adequate method for safeguarding the genetic information about the patient that would flow back to the institution.

b. The institutional IRBs had worries about potential liability arising from the provision of research data from CALGB to the patient.

c. Some institutional IRBs objected to the requirement that the federal government be furnished information concerning the participant that would be maintained for 75 years.

Corrective Action - Accrual: In March, 1996 the Correlative Sciences Core Committee and the Breast Committee discussed actions to correct the above described problem and voted to change the protocol so as to promote accrual. These actions were formalized at the time of the Spring CALGB meeting, May 3-6, 1996 and recommended the following changes to the project:

1. The protocol is to be revised and the consent form is to be changed to indicate that CALGB does not intend to provide patients with results of germ line gene studies.

Rationale: Commercially available tests for familial breast cancer genes are available in the community. CALGB results will be from research tests and the consent instructs patients/physicians not to base medical decisions upon the CALGB derived information. Now that information about familial breast cancer genes is available from commercial sources, there is "no need" for patients to know a CALGB result. Other germ line DNA studies will be performed as a result of this project on these specimens, but the results of these studies will not be relevant to patients care or to counseling with respect to known prognostic or predictive factors.

Since information concerning genetic testing will not be returned to the institution for conveyance to the patient, concern about the handling of this information at the institutional level is no longer an issue.

2. Because of the removal of the requirement that institutions have formal arrangements for provision of genetic counseling, all institutions including those lacking genetic counselors can now participate in this project. Consent forms for all relevant CALGB breast cancer treatment studies will be changed so that the consent for participation in the linked registry studies is given at the same time and in the same setting as the consent for participation in the treatment trial. Informing patients entering treatment trials that they are eligible to participate in the linked registry project will be obligatory.

Rationale: Combining the consent forms for treatment studies and the linked registry will ensure that patients are informed about the linked registry project and have the chance to participate in it. Because the revised consent form has separate sections for the treatment trial and for linked registry participation, patients need not participate in the linked registry if they are not willing to do so. Experience to date indicates that most patients informed about the linked registry project gladly consent to participation in it. Because patients will read a consent form providing them with information about the linked registry at the time they read the consent form for treatment we ensure that patients learn of the opportunity to participate.

3. Because the test results will reside within the CALGB Data Base at Duke University and will not be forwarded to the patient's institution, securing a Certificate of Confidentiality from the Department of Health and Human Services will be more likely.

Rationale: It is unusual for a Certificate of Confidentiality to involve the number of research sites represented within the CALGB (about 200). A Certificate of Confidentiality confers added security to the research information that will be gathered within the linked registry, and will answer some of the concerns raised by institutional IRBs about the security of our data. **Note: A Certificate of**

Confidentiality was issued by the Department of Health and Human Services for this project in July of 1996.

4. The need to educate the Group membership and institutional personnel with respect to the risk/benefits of familial gene studies disappears as a result of these changes. Patients participating in CALGB 9484 need to make an informed decision about whether they will allow collection of blood for germline DNA studies. (They may, nevertheless, participate in 9484 whether germline DNA is collected or not.) However, there is no longer a need for CALGB to ensure that information concerning such testing (now to be confined to that resulting from commercial tests) is presented to the patient in the context of CALGB approved genetic counseling.

Other Actions to Improve Patient Accrual:

1. Requirement that information on research subjects be maintained for 75 years by the federal government: We have been informed during the review of the revised consent form for CALGB 9484 that since this project is viewed by the Army Research and Materiel Command as posing minimal risk to the patients there will be no need to submit long term followup information on participants to the federal government. The consent form has been changed to reflect this.

2. Problems with submission of tissue blocks to our tissue repository in a state where state regulations had been interpreted as prohibiting this activity. A ruling from the New York State Department of Health that the CALGB Pathology Coordinating Office may act as a repository for such specimens was issued August 26, 1996. This eliminates the problem in that state and sets a precedent for other states where this issue could be raised.

Receipt of an Additional Request for Use of Linked Registry:

Dr. James Holland has submitted a description of a project that could benefit from use of the resource provided by the Linked Registry. This request is based upon work at Mt. Sinai Hospital, New York: **Detection of Mammary Tumor Virus ENV Gene-like Sequences in Human Breast Cancer.** This request will be considered by the Tissue Resource Coordinating Committee during the current year.

Progress toward meeting Specific Technical Objectives:

a. To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.

The self completed patient questionnaire contains items from the above sources and additional input from the team led by Dr. Fred Li at the Dana Farber Cancer Institute has occurred so as to yield a questionnaire that meets

the broad needs of investigators. Under the leadership of Drs. Millikan and Ms. Cirrincione a draft self completed questionnaire was developed that addressed the needs of the patients and was capable of being interfaced with the CALGB Data Management System. Pilot testing in CALGB institutions during the early spring of 1995 revealed several problems which were corrected in a further draft that was tested in April. The final version is incorporated in CALGB protocol 9484 which was mailed to CALGB institutions on May 15, 1995 for activation.

The telephone interviews with study participants have gone well and with excellent patient cooperation. Because accrual has been less than anticipated during this period, telephone interviews have been carried out on all patients rather than the originally planned sample. When accrual increases as a result of the changes in the protocol described above, we will return to the original strategy of interviewing a sample of the total population.

Because participants in the amended protocol will not receive information concerning familial gene status, study participants will no longer consist of two groups: those who wish and those who do not wish to know their status with respect to familial cancer genes. Thus portions of the original questionnaire dealing with the topic of the choice to receive information on gene carrier status will be no longer be relevant. The questionnaire has been modified accordingly and pilot testing of these modifications has been successful.

b. To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having two or more relatives with breast, ovarian, or colon cancer.

This technical objective was changed during our budget negotiations prior to activation of the project given the budget limitations. We will not allocate those with a family history of colon cancer into the group for the telephone interview. By so doing we will

(i) enrich for BRCA1 and BRCA2 and potentially AT families, rather than diluting our efforts with potential MMR families,

(ii) avoid overlap with a proposed colon cancer susceptibility study supported by other funding

(iii) allow us to focus (as we should) on breast cancer screening and treatment issues, even though colon cancer is an important disease.

The purpose of developing the selection criteria is to yield a pool of individuals with a family history of breast cancer who will participate in an intensive telephone interview. This hour-long interview was developed with input, not only by investigators from this project, but in concert with others

who have grants from the U.S. Army Research and Materiel Command to support related investigations. In addition, a control group of individuals without a family history of breast cancer who are under treatment on CALGB breast cancer protocols is included, as noted above, for comparison purposes.

c. **To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database. The study will obtain exposure information from affected and unaffected first-degree relatives of patients with a family history of cancer.**

The telephone interviews are proceeding well and there are no problems with this aspect of the study.

As noted above, the interviewing of family members was eliminated from the project prior to study activation as a result of the need to reduce the budget. The investigators in the project are planning to submit a separate application for grant funds to support this aspect of the project. If funded, the questionnaire described above will be administered to family members who participate in the project.

d. **To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine on the above patients and family members.**

CALGB 9484 covering the submission of tissues and specimens listed above, was mailed to CALGB institutions on May 15, 1995. As of September, 1996 the protocol has been approved by the IRBs in the 49 institutions listed in Table 6. When the revised protocol receives final approval by the Army Research and Materiel Command (anticipated by October 1996) we anticipate that the number of participating institutions will increase to about 200.

Table 6
IRB Approval of CALGB Protocol 9484
September 1996

St. Joseph's Hospital and Medical Center, NYH affiliate
University Medical Center - S. Nevada CCOP, UCSD
Valley Hospital Medical Center - S. Nevada CCOP, UCSD
Medical Center of Delaware CCOP, UMCC
Beebe Hospital - CCOP, , part of Delaware CCOP, UMCC
Kent General Hospital - CCOP, part of Delaware CCOP, UMCC
Milford Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Salem County Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Nanticoke Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Riverside Hospital - CCOP, part of Delaware CCOP, UMCC
St. Francis Hospital - CCOP, part of Delaware CCOP, UMCC
Union Hospital of Cecil County - CCOP, part of Delaware CCOP, UMCC
University of Tennessee, Memphis, TN
Baptist Memorial Hospital, CCOP
Roswell Park Cancer Institute, Buffalo, NY
Dartmouth Medical School, Norris Cotton Cancer, (DMS)
VA-White River Junction, DMS affiliate
Springfield Hospital, DMS affiliate
Weeks Memorial Hospital, DMS affiliate

Continuation of Table 6
IRB Approval of CALGB Protocol 9484
September 1996

Northeastern Vermont Regional Hospital, DMS affiliate
Brattleboro Memorial Hospital, DMS affiliate
Cottage Hospital, DMS affiliate
Upper Connecticut Valley Hospital, DMS affiliate
Valley Regional Hospital, DMS affiliate
Androscoggin Valley Hospital, DMS affiliate
Department of Veterans Affairs Medical Center, DMS affiliate
Monadnock Community Hospital, DMS affiliate
Alice Peck Day Memorial Hospital, DMS affiliate
Huggins Hospital, DMS affiliate
Gifford Medical Center, DMS affiliate
The Memorial Hospital, DMS affiliate
El Camino Hospital, Mount Sinai Hospital affiliate
Miriam Hospital, Rhode Island Hospital affiliate
Long Island Jewish Medical Center, (LIJMC)
Winthrop University Hospital, LIJMC affiliate
Salem Hospital, Massachusetts at General Hospital affiliate
Boone Hospital Center, Missouri affiliate
Community Hospital-CCOP, Syracuse affiliate
Monmouth Medical Center, Syracuse affiliate
Eastern Maine Medical Center, Dana-Farber Cancer Institute affiliate
Rutland Regional Medical Center, Green Mountain CCOP, DFCI affiliate
Southwestern Vermont Medical Center, Green Mountain, CCOP, DFCI affiliate
Central Vermont Hospital, Green Mountain, CCOP, DFCI affiliate
North Adams Regional Hospital, Green Mountain, CCOP, DFCI affiliate
University of Chicago Medical Center
Parkview Memorial Hospital, Chicago affiliate
Mercy Memorial Medical Center, Chicago affiliate
Louis A. Weiss Memorial Hospital, Chicago affiliate
Lutheran General Hospital, University of Illinois affiliate

e. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

This activity is proceeding without any problems.

Infrastructure and Policy Development:

Overview:

The Pathology Coordinating Office has developed an integrated coordination and communication network through the Tissue Resource Coordinating Committee for the systematic collection, archiving, surveillance, quality control and quality assurance for the acquisition and processing of the fixed, paraffin tissue blocks for this study. The appointment of a tissue bank coordinator, who also serves as the CALGB Vice Chair and Tissue Bank Coordinator for solid tumor correlative science studies will facilitate and expedite this integration, interfacing with database management, maintaining appropriate quality control and quality assurance procedures for the storage and processing of tissues, and developing policies to respond to institutional pathology concerns of tissue banking. In addition, we have identified coordinating/contact pathologists at each of our main and affiliate institutions to expedite case accessioning of paraffin blocks and to establish a network of communication for responding to mutual concerns and problems that may develop during the course of the study (additional efforts to integrate

pathology participation are discussed section 3). The following sections describe pathology policy that we have developed for tissue banking (see Section A-1 and Appendix 6), and detailed procedures for processing to ensure quality control and quality assurance as well as steps taken to avoid depletion of the block (Appendix 7).

Pathology policy development for tissue banking:

Although tissue acquisition for this study commenced October, 1995, the Pathology Coordinating Office has had experience collecting blocks as a mandatory requirement for four breast cancer clinical trials now active in the CALGB. Because of varying certification and licensing requirements placed at the federal, state and professional society level concerning retention of blocks by institutional surgical pathology laboratories it is not always clear whether all or simply representative tissue blocks are required to remain on file by a pathology laboratory. Some hospital policies prohibit release of an entire block for storage, but will allow cut sections to be stored. Many hospitals are willing to release blocks if they can be assured of accessibility to representative material for any future medical-legal need. In order to address these concerns, and offer alternatives for those hospitals whose policies prohibit release of an entire block for storage, we have developed a Tissue Bank policy for this study (Appendix 6).

Quality control and quality assurance of tissue blocks/sections:

Several precautions are taken to ensure that appropriate processing is performed to accommodate a variety of laboratory uses. High quality sections that are representative of the histopathologic diagnosis of breast cancer are required. For example, to reduce possible DNA contamination for molecular assays the following precautions are taken: gloves are worn by the histotechnician, the disposable blade is wiped down with 10% bleach, followed by 70% alcohol between each block unless a new blade is used; the water bath surface is cleaned between each block, clean forceps are used for each block. In addition, all thick, 10 micron sections cut for molecular assays are placed on uncoated slides (to facilitate scraping) and are stored at 4 degrees. All intact blocks are stored at 4 degrees to minimize antigen deterioration. Thin sections cut for immunohistochemistry are stored at a minimum of 4 degrees (preferably -70°C) and are placed on coated slides (to avoid tissue detachment during assay). H & E sections are cut at different levels throughout the block to ensure that representative tissue is being used for a particular assay. These procedures also address the steps to be taken when minimal tissue is available from the block. This ensures that tissue will not be exhausted in these blocks. A detailed procedure for processing of tissue sections for molecular, immunohistochemical and flow cytometric assays can be found in Appendix 7

Efforts to Integrate Pathologist Participation in this Study:

The institutional pathologist is a critical link for accessing representative tissue for laboratory studies. However, in the cooperative group setting, the pathologist has often not participated in breast cancer studies except in the submission of tumor blocks to the Pathology Coordinating Office. In an effort to enhance integration of pathologists into the cooperative research process for breast cancer clinical trials and correlative science studies, Pathology Workshops are held at CALGB meetings to disseminate information regarding breast cancer studies, to discuss the active role that pathologists can play in these studies and provide a forum for problem resolution with respect to accession and tissue banking. The concept of these workshops and pathology integration in cooperation is fully supported by the College of American Pathology.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB data base and to prioritize use of this information.

This activity is a major goal for years 3 and 4 of this project.

g. To modify the CALGB data base and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.

Under the leadership of Ms. Donna Hollis and Gloria Broadwater, the first half of the above objective has been met. As information concerning these studies is gathered, the second portion of this task will be performed, namely the integration of the information with clinical characteristics, response to treatment and other endpoints.

Further thinking about the research design has indicated that a goal of furnishing the database information to users is inappropriate. Instead, the results of laboratory and other investigations will reside in the database and will be accessed by CALGB statisticians in order to address hypotheses offered by all investigators participating with CALGB in this project.

h. To augment resources at CALGB institutions in order to procure the above described information and specimens.

Payments to institutions to cover the costs of selecting or obtaining specimens has begun. Because accrual has been slower than originally anticipated, the cost to the project for reimbursement of institutional expenses has been less than originally budgeted. With the decision to incorporate the consent for participation in this study into the consent for the

treatment protocol we expect a dramatic improvement in accrual. There will be a corresponding increase in budget from the project to reimburse institutions beginning in 1996 thereby making up the savings during the period of slow accrual.

III. SUMMARY

A. Conclusions:

1. CALGB Protocol 9484, providing the basis for specimen and data collection for a Linked Breast Cancer Registry, has been amended and approved by the Army Research and Materiel Command for review. The amended protocol addresses the principal causes of low accrual to the protocol and approval of the amended protocol is expected shortly. The amended protocol will overcome many of the objections that IRBs raised with respect to the first version of the protocol, and patient accrual to the project is expected to improve rapidly.

2. Problems concerning the nature and process of informed consent for studies of familial breast cancer genes have been addressed during the above process and resolved to the extent that a successful project is anticipated.

3. Personnel responsible for the telephone interview of patients concerning risk factors, exposure and reproductive history, and psychosocial data collection have been hired. The procedures used for this purpose have been developed, pilot tested, revised and implemented.

4. The DNA extraction apparatus has been purchased, installed, and is in use at the University of North Carolina, Chapel Hill. The freezer for urine and plasma samples that was purchased at the Dana Farber Cancer Institute, Boston has been moved to Georgetown University where Dr. Hayes, the subcontractor for this portion of the project, has recently assumed a faculty position. Specimens of plasma and urine are now being shipped to that location.

5. Workshops for CALGB data coordinators and genetics counselors were held November 1995 in Dallas, Texas and May 1996 in Miami, Florida in order to further educate CALGB staff as to the requirements of this project. An additional workshop is scheduled for November 1996 in Pittsburgh.

6. *Changes in Project Staff:*

   Transfer of the CALGB Central Office to the University of Chicago:
   On March 31, 1995, Dr. McIntyre's 5 year term as Chairman of CALGB was completed and he was replaced as Group Chair by Dr. Richard Schilsky, Director of the University of Chicago Cancer Research Center, who had been elected to the position. The Central Office of the Chairman moved from Dartmouth College to the University of Chicago during the week of May 8th. Ms. Karen Sartell the Group Administrator and Ms. Mary Sherrell the Chief Financial Officer who played critical roles in this project at Dartmouth continue in these positions in Chicago and continue their important roles within this project. A new protocol

editor in Chicago, Kathleen Karas, has replaced Priscilla Stoner who contributed to this project at Dartmouth. The effort devoted by those in the Central Office to this project has not changed and the positions previously supported at Dartmouth are now supported by a subcontract to the University of Chicago from Dartmouth. Dr. McIntyre continues as Principal Investigator and is linked to the Central Office in Chicago by e-mail, FAX, phone, and by frequent meetings with the staff of the Central Office. During the 1995-1996 project year these arrangements have proved very satisfactory and will be continued in the next year of the project.

As a result, there has been no material effect of the change in the location of the Central Office upon this project. Nor has there been any change in the time-line as a result of the move of the Central Office. There will be no change in the cost of the project. **A letter of support for this project from Dr. Schilsky supporting the project is included as Appendix 8.**

Dr. Liu assumed the position of Director of the Division of Clinical Sciences, National Cancer Institute and departed from his previous position at the University of North Carolina, Chapel Hill (UNC) during the summer of 1996. Lynn Dressler, M.A. who has played a major role in the project at that institution has been appointed to take over the responsibility for the subcontract at UNC. This transition has been very smooth and no problems are anticipated because of Dr. Liu's departure. Dr. Liu will continue to interact with his laboratory at UNC weekly during the next year.

Dr. Daniel Hayes, moved from the Dana Farber Cancer Center, Boston, to the Lombardi Cancer Center at Georgetown University, Washington, D.C. The specimens, laboratory equipment and subcontract supporting his participation in this project have been moved to this new location and there were no problems with this transition.

B. Changes Resulting from Experience in Year 2. Problems and Corrective Actions.

The major problem during year 2 has been the slower than anticipated accrual to CALGB 9484 due to the ethical issues surrounding the studies of familial cancer genes. The initial version of our protocol was developed as a consensus regulations concerning use of human subjects and cancer advocates. Despite this input, there has been much slower than expected activation of the protocol at our institutions. Although our project was conceived and designed to minimize the risks involved in this kind of research, the appearance of cautionary articles for the lay and scientific community [27] resulted in a changed climate for the institutional review of this project. Although a number of IRBs have approved the protocol, the protocol has been approved in only about one sixth of CALGB institutions.

Further education efforts will take place at a workshops to be held during the CALGB 1996 Fall and 1997 Spring meetings. These education efforts promote accrual and address other issues that come up as the study progresses. These workshops will continue at future CALGB meetings.

At this time, we are behind the schedule set out in the budget revision negotiated at the time this project was activated. In order to move the project along at a faster rate it was necessary for us in the last year to assign additional personnel at the University of North Carolina who have worked with the staff at the CALGB Pathology Office at Roswell Park Cancer Institute in order to gear up for more rapid receipt of specimens in year 3. In addition, equipment purchases planned for the CALGB Pathology Office will assist in more rapid processing of specimens.

An unexpected number of institutions have requested that the blocks submitted on 9484 be returned immediately after sections have been taken and have cited various regulatory or legal requirements as the reason for these requests. In order to resolve this problem we are taking two courses of action. We hope to convince most of those making this request that it is reasonable for us to have custody of their blocks as long as we demonstrate that we can return them to the institution within one business day of a request for their return. Second, we plan to maintain paraffin sections at 4°C or colder In addition, we indicate, on the slide, the date the sections were cut to help address there issues. We are also conducting time-course experiments to optimize storage conditions for new antibodies as they become available for use. This may stabilize antigens that have been shown to deteriorate in sections maintained at the higher temperature.

A Certificate of Confidentiality has been granted from the Department of Health and Human Services HHS in order to enhance the level of confidentiality concerning the results of the testing for hereditary cancer genes resulting from this project.

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APPENDIX 1

CALGB Protocol 9484
Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

__X__ **Revision** __X__ **Amendment** ____ **Status Change**

__X__ Change of participants/coordinator (s) +/-

__X__ Editorial, administrative changes

__X__ Scientific changes (IRB approval)

_____ Therapy changes (IRB approval)

_____ Eligibility changes (IRB approval)

__X__ Informed Consent changed (IRB approval)

_____ Other:

____ Activation

____ Closure

____ Partial Closure

____ Temporary Closure

____ Reactivation

Due to the extensive changes made to this study, a replacement document is being issued at this time. Please discard the previous version of this protocol, including the model consent form. The appendices, however, should be retained, except for the following: replace the CALGB Detailed Family History and Epidemiology Telephone Interview in Appendix II with the updated version in this update, and add new Appendix IV, DHHS Confidentiality Certificate.

Note: The C-449 form for urine collection is not included in this mailing but will be issued in a subsequent mailing. If you need a C-449 form in the interim, please contact the CALGB Data Management Center, 919-286-0045, x221.

SUMMARY OF REVISIONS:

Address and phone numbers have been updated for Dr. McIntyre, Study Chair, Breast Committee Chair, Data Coordinator, and Dr. Hayes. ***PLEASE NOTE THAT ALL URINE AND BLOOD SHIPMENTS TO DR. HAYES SHOULD BE SENT TO LOMBARDI CANCER CENTER, NOT DANA FARBER CANCER INSTITUTE. EFFECTIVE WITH THIS UPDATE, URINE COLLECTION SHOULD BEGIN AS SPECIFIED IN THE PROTOCOL.***

The telephone area code for the Central Office has been changed; the fax number, however, remains the same.

Specimen procurement and shipping instructions have been clarified throughout the protocol.

The Department of Health and Human Services has issued a Confidentiality Certificate for this project; a copy is included as Appendix IV.

SUMMARY OF AMENDMENTS

Test results will no longer be provided to patients or their physicians. The tests conducted by the CALGB are intended for research, not diagnostic, purposes. Commercial tests are now available for those patients who wish to pursue this option after consultation with their physician. Since the results of research tests will no longer be provided to the institution, the requirement for comprehensive genetic counseling services has been dropped.

All references to registration of family members and studies of family members have been deleted, as these studies will not be pursued at this time.

There is no longer a free-standing consent form for 9484. Instead, the essential elements of consent for 9484 have been incorporated into the treatment protocol consent forms. The model consent sections are included in this protocol for reference only. Please see amendments dated 10/15/96 for protocols 9082, 9342, 9343, and 9344 and submit these revised treatment protocol consent forms to your IRB. Patients will be presented with all options included in the revised treatment consent form: collection of tissue, blood, urine, completion of questionnaires, and the separate section regarding the use of specimens to study heritable genes. Patients who agree to collection of tissue, blood, urine and the completion of questionnaires must initial these items within the treatment consent form as directed; patients who agree to have their specimens studied for heritable genes must sign the section of the treatment consent form entitled "Consent for Studies of Heritable (Familial) Cancer Genes". Registration to 9484 for those patients agreeing to these additional items should take place simultaneously with registration to the treatment protocol. Patients who agree to have their specimens collected, but refuse to have them studied for heritable genes, may still be entered on 9484. Questions regarding eligibility should be directed to the study chair, Dr. McIntyre, or to the Central Office (contact Kathleen Karas, protocol editor.)

This update contains Cover page through page 16, an updated CALGB Detailed Family History and Exposure Telephone Interview (Appendix II), and Appendix IV, DHHS Confidentiality Certificate.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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cc: O. R. McIntyre, M.D., L. Norton, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., M. Barcos, M.D., L. Schnaper, M.D., D. Berry, Ph.D., L. Dressler, M.A., R. Millikan, DVM, Ph.D., L. Gross

CANCER AND LEUKEMIA GROUP B

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

CALGB 9484

Companion to CALGB 9082, 9342, 9343, 9344

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For questions regarding submission of tissue samples, contact:

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Roswell Park Cancer Institute
Department of Pathology
Elm at Carlton
Buffalo, New York 14263
Phone: (716) 845-4443 Fax: (716) 845-8077
calgbpath@sc3102.med.buffalo.edu

For questions regarding submission of whole blood samples, contact:

Lynn Dressler, M.A.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Phone: (919) 966-0196 Fax: (919) 966-4244
dressler@med.unc.edu

For questions regarding submission of plasma and urine samples, contact:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
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3970 Reservoir Road, NW
Washington, DC 20007
Phone: 202-687-2103 Fax: 202-687-4429
hayesdf@gunet.georgetown.edu

For questions regarding forms, contact:

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Data Coordinator
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TABLE OF CONTENTS

Pages have been renumbered for Appendix 1, 10/1/95 - 9/30/96 Progress Report.

1.0 INTRODUCTION

This project involves the collection of tumor specimens, genomic DNA, and information concerning medical, reproductive, exposure and family history from patients with breast cancer. The purpose is to create a library in which clinical information on groups of uniformly staged and treated patients on CALGB protocols is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based tumor registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It will be possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[1]

We have termed this resource a "specialized registry". The specimens (breast cancer tissue, plasma, urine, or in some cases, DNA) will be made available to qualified investigators who will conduct a variety of research projects that test laboratory-based, psycho-social or epidemiological hypotheses. These investigators will be supported by peer-reviewed grants and other mechanisms, and the studies will be done at no charge to patients. Laboratory results will be forwarded to the CALGB database where CALGB statisticians will be responsible for all analyses. All information resulting from these studies will reside in the CALGB database and all patient identifiers will remain confidential within the CALGB Data Management Center.

Population-based studies are not included at this time: with all of the ethical and legal ramifications inherent in population-based genetic studies, we feel that this type of study should come later when specific hypotheses are more fully formed and after we have established the scientific and psycho-social framework for communicating this type of information to the general public.

Ethical and legal issues relating to studies of heritable genes, and submission of tissue: Based upon policies adopted by the CALGB concerning studies of heritable cancer genes, a separate prospective informed consent for genomic DNA submission, as well as consent for participation in the other components represented, is required. These consent documents are incorporated into the consent documents for each relevant treatment protocol. Consent to participate in the specialized registry must be obtained at the time the patient enters the treatment study.

With respect to submission of fixed tissue blocks after diagnosis has been established at the local institution, there are a number of unresolved and sometimes conflicting issues that are currently being addressed by appropriate bodies. The "ownership" of the tissue blocks is felt by some to have been conveyed to the institution by the wording of the usual consent for surgery, but this is disputed by others who feel that, for the purposes represented by the studies to be performed via this protocol, the patient retains rights to the tissue. More particularly, the view has been expressed that the patient may have an enforceable privacy interest when studies are done on tissue that is linked in some manner to them.[3] We believe that the consent for the specialized registry included in each relevant treatment consent form specifies conditions in which the patient's right to privacy is not subjected to a new risk with each new use of the registry. State laws, the American College of Pathology, the Joint Commission on the Accreditation of Health Care Facilities, and the Clinical Laboratory Improvement Act (CLIA) may have requirements concerning retention of diagnostic tissue at the local institution, and it remains to be determined whether it is permissible under these policies to place the tissue in the custody of other approved parties. Finally, there are divergencies of opinion between the U.S. Army Medical Research and Materiel Command and the Office of Protection from Research Risks, National Institutes of Health, concerning a requirement that specimens collected with

funding from the Department of Defense become the property of the U.S. Government. Certain of these may require establishment of legal precedent for their resolution. Institutions with concerns about this possibly conflicting positions may wish to contact Dr. Maurice Barcos, Director of the CALGB Pathology Coordination Office, for additional information about the procedures that CALGB has established to ensure that fixed breast tissue remains available for return to the institution, if required.

2.0 OBJECTIVES

1. To collect formalin-fixed, paraffin-embedded (FFPE) breast tissue for in situ studies and extraction of somatic DNA and peripheral blood for extraction of germline DNA, also plasma and urine from patients with breast cancer entered on CALGB breast cancer treatment protocols.

2. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

3. To gather key family, endocrine and reproductive history, and exposure data on the above patients.

4. To prepare and submit the above specimens to approved investigators who will perform various laboratory studies on them and provide the results to the CALGB database for correlation with clinical data and patient outcome.

5. To analyze the data resulting from the above activities in order to seek new knowledge about etiology and progression of breast cancer.

3.0 STATISTICAL CONSIDERATIONS

A Steering Committee is responsible for approving each individual project using the resources of the specialized registry. Each individual project submitted for review will contain a statistical section detailing the hypothesis and the estimated powers required in the proposed analyses. Flexibility is essential since the alternative hypothesis will vary from one project to the next. If the alternative hypothesis is close to the null, then a large number of patients will be required. A major element in the Steering Committee's review of the proposal will be whether the hypothesis may be adequately tested given the current resources of the registry.

Many of the proposals that we expect to receive will concern analyses of subgroups of patients within the registry. These would be conducted by evaluating an ordered list of scientific hypotheses using sequential statistical tests and would facilitate an early decision on whether a new hypothesis was worth further investigation, while avoiding wasting too much biological material on testing hypotheses that may eventually prove unfruitful. This method will also help to distinguish between a "multitude of hypotheses".[4] The value of the registry to the investigators will be enhanced if it is sufficiently large to allow them to test their hypotheses on subgroups of sufficient size so that adequate power is obtained to detect the differences which are sought. For this reason, the larger the number of patients represented in the specialized registry, the more useful the registry will be. It is anticipated that the alternative hypothesis will dictate power, and allocation of resources will proceed sequentially. There is a wealth of material on case only analyses, in which comparisons of cases only (no controls) are used to evaluate gene-environment interactions.[5] We have planned for a registry of up to 5,000 individuals but this number may be adjusted upwards or downwards without amending the protocol depending upon the experience with the various users and the ability to secure funds to operate the registry.

4.0 ELIGIBILITY CRITERIA

4.1 The patient must be enrolled on a CALGB breast treatment protocol. Those protocols from which patients may be entered are listed below. This list will be modified in updates (revisions) to this protocol to include additional CALGB adjuvant or metastatic breast cancer treatment protocols that are activated during the funding period.

9082 A Randomized, Comparative Study Of High Dose CPA/cDDP/BCNU and ABMS Versus Standard Dose CPA/cDDP/BCNU as Consolidation to Adjuvant CAF for Patients with Operable Stage II or Stage III Breast Cancer Involving ≥ 10 Axillary Lymph Nodes

9342 A Phase III Study of Taxol at Three Dose Levels in the Treatment of Patients with Metastatic Breast Cancer

9343 Evaluation Of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy Plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast that is Less Than or Equal to 4cm and Clinically Negative Axillary Nodes: A Phase III Study

9344 Doxorubicin Dose Escalation, With Or Without Taxol, As Part Of The CA Adjuvant Chemotherapy Regimen For Node Positive Breast Cancer: A Phase III Intergroup Study

4.2 Patients must initial the appropriate portions of the consent form agreeing to have their archived tissue blocks, (including somatic DNA but excluding analyses of germline genetic characteristics on associated normal tissues), plasma, and urine submitted for study and to participate in collection of family, exposure and endocrine history questionnaires. Note: If the patient also consents to participate in genomic studies, cells for genomic DNA must be obtained prior to the first radiation or chemotherapy treatment.

5.0 REGISTRATION

Registration will be accepted through the Main Institution only. Confirm eligibility criteria (Sec 4.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 am-5 pm Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient' s Social Security #
Patient' s Name, I.D.#
Patient's Address and Phone Number
Signed Informed Consent (Date)
Type of consent signed: Genomic studies, Non-genomic studies
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (Sec. 4.0) (yes, no)
List CALGB treatment protocol
Does patient release or retain rights to specimens?
Date of most recent Institutional Review Board approval (<1 year)

6.0 REQUIRED DATA

6.1 Submit data forms and specimens according to protocol requirements for all patients registered on CALGB 9484 who receive treatment on an appropriate CALGB breast treatment protocol.

6.2 CALGB institutions should submit specimens along with their corresponding pathology/specimen submission forms to the appropriate CALGB laboratory for storage, as indicated below. If tissue block will not be submitted for a patient, the institution should submit the CALGB Pathology Routing Form (C-350) indicating the reason for nonsubmission along with a letter from the institutional pathologist explaining the reason for nonsubmission.

Copies of these forms are included in this appendix.

6.2.1 Submit **tissue block** (or letter stating why tissue block will not be submitted), surgical path report and **original** C-350 form to:

Maurice Barcos, MD, PhD
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263-0001

and a copy of C-350 form to the CALGB DMC; keep a copy for your records.

6.2.2 Submit **whole blood** specimens with **original** C-383 form to: **(NOTE: PATIENT MUST HAVE SIGNED CONSENT FOR STUDIES OF HERITABLE GENES)**

Qing Yang/Daynice Skeen/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7295 Lineberger Cancer Research Center
Mason Farm Road, Room 350
Chapel Hill, NC 27599-7295

and a copy of C-383 form to CALGB DMC; keep a copy for your records.

6.2.3 Submit **plasma** specimens with **original** C-384 form to:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-384 form to CALGB DMC; keep a copy for your records.

6.2.4 Submit **urine** specimens with **original** C-449 form to:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-449 form to CALGB DMC; keep a copy for your records.

6.2.5. Send Family History of Cancer Questionnaire to the CALGB DMC:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705

7.0 DATA SUBMISSION

FORM		Submission Schedule
C-350	CALGB Pathology Routing Form (for tissue blocks) Surgical path report	Submit both form and report regardless of whether or not block is sent. Submit with either tissue block from surgical specimen (breast or node) OR letter from pathologist stating reason for nonsubmission of block. Submit prior to first chemo/RT treatment.
C-383	CALGB Specimen Routing Form (for whole blood)	Submit with whole blood specimens. Submit prior to first chemo/RT treatment.
C-384	CALGB Specimen Routing Form (for plasma)	Submit with plasma specimen. Submit prior to first chemo/RT.
C-449	CALGB Specimen Routing Form (for urine)	Submit with urine specimen. Submit prior to first chemo/RT. For adjuvant studies using chemotherapy, submit prior to treatment, at the completion of treatment, and at each follow-up visit scheduled in the treatment protocol. For adjuvant studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol. For metastatic studies using chemotherapy, submit prior to treatment, on day one of each cycle, and at each follow-up visit scheduled in treatment protocol. For metastatic studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol.
C-377	Family History of Cancer Questionnaire	Within 2 wks of registration onto CALGB 9484. If the patient declines to complete the questionnaire, it should be submitted with "PATIENT DECLINED" and the date written across the top.

8.0 METHODS

8.1 ***Patient entry:*** Eligible patients are entered on this protocol if they consent at the time they are enrolled on the treatment protocol and meet study eligibility requirements given in section 4.0.

8.2 ***FFPE tissue:*** A representative block of the primary tumor is best for biologic markers and histologic correlations, but both primary and nodal tissues are acceptable for biologic assays. If insufficient primary or nodal tissue is available for submission of one block, a brief explanatory note from the institutional pathologist within six months of patient entry will suffice.

Submission of representative tissue sections on glass slides is not acceptable since the tissues must be processed in different ways for various assays: 4μ on glass slides for HE staining and immunohistochemistry, 10μ for DNA extraction, and 30μ for nuclear isolation for flow cytometry. The CALGB Pathology Office at Roswell Park Cancer Institute will prepare these sections as there is some evidence that antigen loss may occur over time on cut sections unless maintained at a low temperature.

Each submitted block will be carefully protected and monitored by the CALGB Pathology Office so that depletion of the block is minimized and a minimum of three recut HE sections remain on file at all times. National Institutes of Health directives call for the indefinite retention of each submitted block for future, as yet undetermined, biologic/genetic assays. Upon request for any emergent clinical or legal reason, the remaining portion of the block and one HE section will be returned by overnight mail to the originating Institutional Pathology Laboratory .

Tissue blocks from the operative (not needle biopsy) specimen along with the corresponding surgical pathology report and original Form C-350, CALGB Tissue Routing Form must be submitted to:

Dr. Maurice Barcos, Chair
CALGB Pathology Office
Roswell Park Memorial Institute
Department of Pathology
Elm and Carlton Streets
Buffalo, NY 14263
716-845-4443

Institutional data managers will arrange for submission of tissue blocks to the above address by contacting the appropriate pathologist at a CALGB main member or affiliate institution.

Somatic DNA: From the specimens collected as described above, individual investigators will prepare DNA according to their established laboratory procedures. It is anticipated that somatic DNA will be derived from the tumor specimen, but somatic DNA abnormalities may also be sought in normal tissue adjacent to the tumor.

8.3 Timepoints for collection of plasma, urine, and whole blood for genomic studies:

8.3.1 For Adjuvant studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, at the completion of therapy, and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.2 For Adjuvant studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.3 For Metastatic Studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, on day one of each cycle of treatment, and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.4 For Metastatic Studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.4 Collection and handling instructions for plasma, urine, and whole blood for genomic studies

8.4.1 Plasma collection and handling:

Collect 10cc of whole blood by venipuncture into an EDTA-containing (purple top) collection tube.

Centrifuge blood at 3000Xg for ten minutes (standard clinical centrifuge). Then aliquot supernatant plasma into a separate tube and label the tube with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the plasma should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-384 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.2 Urine collection and handling:

Collect 50 ml (or more) clean catch urine into sterile urine collection container.

Centrifuge urine at 200g for 3 minutes (standard clinical centrifuge).

Pour spun urine into plastic freezing tube and label with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the urine should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-449 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.3 Collection of whole blood for Genomic DNA studies:

Genomic DNA: Note: A separate portion of the consent form used for treatment studies must be signed for studies of genomic DNA.

One to two 8cc tubes of whole blood should be drawn in yellow topped tubes (Vacutainer #4606; acid-citrate dextrose solution). Two tubes are preferable. Collect and store tubes at ambient temperature (70°F, 25°C). Blood should **NOT** be refrigerated but should be stored in a cool place. Blood should be shippted within 24 hours of collection, at ambient temperature. Cold packs are not required. An original C-383 form must be submitted with each sample, with a copy of the form sent to the DMC. Ship to:

Qing Yang/Daynice Skeen/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7295 Lineberger Cancer Research Center
Mason Farm Road, Room 350
Chapel Hill, NC 27599-7295

Note: Blood samples should be sent by overnight carrier, Monday through Thursday. (For Thursday shipment, please send by priority overnight.) **DO NOT SHIP BLOOD ON FRIDAYS OR THE DAY BEFORE A HOLIDAY.**

If it is absolutely necessary to draw blood on a Friday or the day before a holiday, keep the blood at ambient temperature. Blood should be shipped within 72 hours. Therefore, blood drawn on a Friday should be shipped on Monday by overnight carrier for Tuesday delivery.

The UNC DNA Extraction Laboratory will perform leukocyte separation and DNA extraction. Lymphocyte DNA will be prepared using the ABI DNA extractor and the DNA stored at -70°C. The methods to be employed are those already in place for studies of ras mutations in leukemic cells by the CALGB.

8.5 **Shipment billing:** Federal Express forms with a pre-printed account number for this study are available from the main member institution. This account number should be used exclusively for shipment of specimens as detailed above. Main member institutions can obtain additional pre-printed Federal Express forms by contacting the Protocol Assistant at the CALGB Central Office: 312-702-9171.

8.6 **Self-Administered Family History of Cancer Questionnaire:** After the patient gives informed consent and is registered to CALGB 9484, the patient will be given a self administered questionnaire covering the above topic. The questionnaire requires a short time to complete and should be submitted within 2 weeks of entry onto CALGB 9484. The institutional data managers should use the self-addressed envelope to send the completed questionnaires to:

CALGB Data Management Center
2200 West Main Street, Suite 430
Durham, NC 27705
Phone: 919-286-0045
Fax: 919-286-1142

The CALGB DMC will forward a copy of the questionnaires to the Specialized Registry staff at the Epidemiology Office of the University of North Carolina.

A sub-sample of patients identified on the basis of information provided by the self-administered questionnaire (CALGB Family History of Cancer Questionnaire) will be contacted by the epidemiology office staff at the University of North Carolina, Chapel Hill, and asked to complete a more extensive phone interview (CALGB Detailed Family History and Exposure Telephone Interview). The participating epidemiology staff is funded by a grant, so the phone interviews will be conducted at no charge to patients or their families. Prior to contacting patients by phone, the epidemiology staff will contact the institution that registered the patient to assure that the patient is still alive and not hospitalized, in order to minimize stress to the patient and/or family.

8.7 **Receipt of Specimens:** A system is being implemented so that Centers receiving specimens will electronically report to the CALGB database the receipt and condition of the specimen using standard CALGB procedures. However, until this system is fully operational, initiating Centers will e-mail or fax this information to the responsible data coordinator at the Data Management Center.

8.8 Tracking of Patient Specimen Submission: The CALGB data management system (or data coordinator, until the system is fully implemented) will track patients who are entered on this CALGB protocol and generate reminders to institutions that have entered patients on this protocol if the specimens are not received at the appropriate office or lab in a timely manner.

8.9 Training of data managers: On a regular basis, not less than once a year, a portion of the CALGB Clinical Research Associates workshop will be devoted to instruction of the proper methods of obtaining and shipping the above specimens.

8.10 Specialized Registry Policies: Application for use of Registry. Use of the registry is under the supervision of the Specialized Registry Steering Committee appointed by Dr. O. Ross McIntyre, M.D. the Principal Investigator on the grant from the U.S. Army Medical Research and Materiel Command which supports the registry. Charter members of the Steering Committee are listed below:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Chairman.	Dartmouth Medical School
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Larry Norton, M.D.	Br. Com. Chm	Memorial Sloan-Kettering
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS
Daniel Hayes, M.D.	Vice Chm. Br. Com.	Dana Farber
Judy Garber, M.D.	Member, Cor Sci	Dana Farber
Alice Kornblith, Ph.D.	Member, Psy Onc	Memorial Sloan-Kettering
Deborah Collyar	Patient Advocate	
Sue Moore	Patient Advocate	

Additional members may be appointed to the steering committee from time to time and will be noted in revisions to this protocol. However, it is anticipated that there will be minimal turnover of steering committee membership.

Laboratory and epidemiological studies that are approved by the Steering Committee for the use of the Specialized Registry will be kept on file at the CALGB Central Office and incorporated into this appendix. Each project will have received IRB approval at the submitting investigator's institution. Individual projects will not require IRB approval at individual CALGB institutions.

Procedures for Project Approval/Appendix Inclusion: Investigators wishing to use the resources of the registry must apply to the Steering Committee for permission to obtain materials or information from the registry. In each case the investigator must submit a protocol for the proposed study and furnish evidence that it has been reviewed and approved by the Institutional Review Board at the investigator's institution. In addition, the investigator must accept other conditions governing the collaboration. If the investigator is a member of CALGB, usual policies governing Group data management and publication will prevail. If the user is not a member of CALGB, a CALGB co-chair of the proposed study will be appointed by the Steering Committee in consultation with the investigator. The person serving as co-chair will assist in trouble-shooting and will present a synopsis of the status of the study at CALGB meetings, if the non-CALGB investigator is unable to attend. The investigator will be asked to sign a letter outlining the essential features of the collaboration with the Specialized Registry. An important feature of the collaboration is that the investigator will furnish results to the CALGB Data Management Center where analyses will be performed by the CALGB statistician. No information concerning the patient, other than the specimen from an individual on a CALGB trial, will be furnished to the investigator. In this manner the laboratory will remain blinded as to

the other information available about the patient and patient confidentiality will be protected as well. The letter stipulates that the investigator will not provide specimens received from the registry to third parties. These procedures have been put in place in order to: protect patient confidentiality; blind the laboratory doing tests with respect to patient outcomes until the laboratory has submitted its results and the responsible CALGB statistician has performed an analysis; and achieve agreement on the presentation and publication of results prior to commencing with the work.

It is anticipated that the Specialized Registry will be used by a large number of investigators. This protocol will not be amended to describe the details of each laboratory or other use to which an approved investigator may put the Registry. however, as stated above each project using the Registry will have received IRB approval at the investigator's institution. It is anticipated that methodologies in the laboratories will be rapidly evolving during the lifetime of the Registry and that a number of hypotheses will be offered in the future that could not be conceived today. The patients have been given assurance that the Registry will approve studies that are limited to those involving cancer, and it is not intended to reconsent the patient for each new test for which the registry will be used.

Studies of heritable cancer genes will be conducted according to CALGB policies for the studies of such genes.

9.0 REFERENCES

1. Rothman K. Modern Epidemiology, pp 95-96, Little Brown, Boston, 1986.

2. Khoury M, James L. Population and familial relative risks of disease associated with environmental factors in the presence of gene-environment interactions. Am. J Epidemiol. 137:1241-50, 1993.

3. Charrow RP. Bench Notes- Judgements: Whose Tissue is it, Anyway? Jr. NIH Research, 6: 79-81, 1994

4. Kaaks R, Tweel I, van Noord P, Riboli E. Efficient use of biological banks for biochemical epidemiology: exploratory hypothesis testing by means of a sequential t-test. Epidemiology 5: 429-38, 1994.

5. Begg C, Zhang Z. Statistical analysis of molecular epidemiology studies employing case-series. Cancer Epidemiology Biomarkers & Prevention 3: 173-75, 1994.

10.0 MODEL CONSENT SECTIONS FOR ELIGIBLE BREAST CANCER TREATMENT PROTOCOLS

NOTE: THE FOLLOWING SECTIONS WILL BE INCORPORATED INTO ELIGIBLE TREATMENT PROTOCOL CONSENT FORMS. THERE IS NO LONGER A SEPARATE CONSENT FORM FOR CALGB 9484. THE MATERIAL BELOW IS INCLUDED FOR REFERENCE ONLY.

(THE FOLLOWING SECTIONS ARE FOR CALGB INSTITUTIONS ONLY; PATIENT AND WITNESS SHOULD INITIAL AND DATE EACH PAGE)

Other research being done in connection with this project: The United States Army Medical Research and Material Command is supporting CALGB research concerning the causes of breast cancer and its response to various treatments. The following part of this consent form has been approved by the U.S. Army and contains certain statements required in consents for research conducted with support from the Department of Defense.

Collection of tissue, blood and urine: This protocol provides for the collection and use in research of portions of tissue obtained at the time of your surgery for breast cancer. With your permission, blood and urine will also be collected and stored for future research conducted by investigators working with CALGB. The tissue, blood and urine samples collected will form a "registry" of material to be used for breast cancer research. Urine and blood samples will be obtained during routine urine and blood tests performed for your care, including before your treatment begins, after your treatment is completed, and at other times during your treatment and follow-up care. About one-half cup of urine and one extra tube of blood, about 1-1/2 tablespoons, will be sent to a central laboratory where it will be stored and used for breast cancer research. There will be no additional cost to you as a result of obtaining the tissue, blood, and urine samples used in this study.

Benefits: You are not expected to benefit personally from participation in these studies involving tissue, blood, and urine samples. Your participation may help investigators to better understand breast cancer and lead to improved treatment for future breast cancer patients.

Confidentiality: Information about your participation and test results will be stored only at the CALGB Statistical Office at Duke University. This information will not be put in your medical records and will not be available to you, your doctors, or to individual researchers in CALGB. All information is stored under conditions to protect the privacy of study participants. In our analyses, you will never be listed by name. The results of these studies may be published, but individual patients will not be identified. Representatives of the U.S. Army Medical Research and Material Command, the sponsor of this study, may review research records as a part of their responsibility to protect human subjects in research.

I give permission for my tissue_____ blood_____ and urine_____ to be collected for research purposes (please initial each item for which you grant permission. If you do not give permission for any of these specimens, leave blank.)

Retention of rights: You are permitted to retain rights to any commercial application that may arise because of the use of your specimens in this project. Retention of these rights, however, increases the cost and paperwork for the CALGB and for the granting agencies supporting this research. Because of this you may wish to sign the statement below:

I voluntarily and freely donate any and all blood, urine and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items:

_____Yes ____No Initial_____

Questionnaire: If you consent, you may be asked to participate in studies that attempt to assess the quality of life during and after treatment. We request that you take a few minutes to complete a questionnaire providing information about cancer in your family. On the basis of this questionnaire, a trained interviewer from CALGB may call you and ask you if you are willing to answer additional questions.

I agree to complete the questionnaire and give permission to be contacted by phone, if chosen for an interview: If yes, initial here:_____

Use of these specimens: Because it is impossible for you, your doctors, or CALGB to know what laboratory tests may be discovered in the future, you have given your permission for such studies to be performed without restrictions except as noted in this consent form, and do not wish to be contacted for permission to conduct each specific test. Investigators wishing to perform research using samples collected in this study must first receive approval from the CALGB Steering Committee for this project, and agree in writing that the samples will be used only as agreed upon by the CALGB. The registry will be used only for studies on or related to breast cancer. Neither you nor your doctors will receive the results of these research tests.

Statements required by the granting agency: The United States Army Medical Research and Materiel Command which supports the registry functions described above, not your treatment, requires the statements that follow in this section. These statements pertain only to the registry function described above, not your treatment for breast cancer on the clinical trial that you are entering.

"You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research. Contractors must provide such medical care when conducting research on private citizens. Other than medical care that may be provided there is no compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights."

By signing below, you indicate that you have read this form, received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

(Patient's Signature)	(Date)	(Name of Responsible Investigator	(Phone #)
(Physician's Signature)	(Date)	(Name of IRB Representative)	(Phone #)
(Witness's Signature)	(Date)		

CONSENT FOR STUDIES OF HERITABLE (FAMILIAL) CANCER GENES:

In addition to the studies above, the registry will be used for studies of cancer genes that can be inherited. A number of factors contribute to the risk of developing breast cancer. Some of these are cancer susceptibility genes that are carried from one generation to the next in certain families. These appear to cause a small fraction of all breast cancer cases. We ask that you agree to participate in our studies of genes that may be involved in the evolution of breast cancer. It is not likely that information generated from our studies will be of benefit to you individually. However, your participation in this study may help us to better understand breast cancer and lead to a benefit for future patients.

Risks, Safeguards, and Reduction of Risk:

There are no absolute legal protections against discrimination on the basis of genetic information. For this reason, CALGB will treat all studies using these specimens as **research only, and will not furnish results of the analyses to anyone, including you or your physician.** Instances are known in which a patient has been required to furnish genetic information as a precondition for application for health insurance and/or a job. Participation in this study **does not** mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your physician. If you are interested in having genetic testing performed, you should consult your physician, as commercial tests are available. Your physician can provide you with the necessary information to determine if such a test would be appropriate for you.

Research laboratories that test your blood will not be given any information about you. Information about your participation and about the results of these tests will be stored only at the CALGB Statistical Office at Duke University. This information will not be made available to your doctors or to individual researchers in CALGB. This information will not be put in your medical records. All information in the CALGB computer is stored under conditions which limit access in order to protect the privacy of study participants. Information on the presence or absence of familial cancer genes will be stored in separate files with the highest level of security and linked with the rest of your data only for the performance of statistical analyses that are carried out under the direction of CALGB statisticians. As indicated above, these analyses will not list you by name.

If you decide not to allow your specimens to be used for studies of cancer genes that can be inherited, you should **not** sign this section of the consent form. However, you may still agree to donate tissue, blood and urine for studies of traits that cannot be passed from one generation to another, and to complete the questionnaire.

Method: As part of providing your care and adjusting your treatment your doctor will be drawing routine blood tests on a regular basis. With your approval, three extra tubes of blood will be drawn (about 5 tablespoons) once during routine blood tests performed before you begin your treatment. You should experience no extra discomfort or side effects. Your blood specimen or non-cancerous cells that were removed at surgery will be the source of DNA that will be used for research studies, including studies of genes that are passed from generation to generation. Your DNA will become the property of the CALGB specialized registry and may be shared with investigators from a number of qualified academic institutions that are studying the genetic causes of cancer. Specimens shared with these investigators will not by identified by patient name.

I hereby give my permission for a blood sample to be obtained that will allow for the study of my genes, including possible family cancer genes. I understand that results of the research studies will not be made available to me or my physician.

(Patient's Signature)	(Date)	(Name of Responsible Investigator)	(Phone #)
(Physician's Signature)	(Date)	(Name of IRB Representative)	(Phone #)
(Witness's Signature)	(Date)		

APPENDIX I

Data Collection Forms

C-350 CALGB Pathology Routing Form

C-383 CALGB Specimen Routing Form: Whole Blood

C-384 CALGB Specimen Routing Form: Plasma

INSTRUCTIONS FOR
CALGB PATHOLOGY ROUTING FORM (C-350)

A. Purpose

To provide identifying information that will acccmpany the slides, paraffin blocks, and pathology report submitted as per protocol.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.)

3. Code whether the specimen is being sent with this form. If the specimen is not sent be sure to record the reason why it is not being sent (i.e. not enough tissue available, poor specimen quality, etc.). The pathologists at your institution will be able to provide this information.

4. Record the month, day, and 4-digit year that this report is being submitted.

5. Record the number of pathology reports attached.

6. If slides are included, record the number of slides being submitted in the appropriate space. If blocks are included, record the number of blocks being submitted in the appropriate space. This will aid the CALGB pathology office in returning the correct number of specimens to the submitting institution.

7. The full name of the responsible investigator and pathologist and the patient's surgical pathology number at the treating institution should be recorded on the lines provided. This information will further aid in properly identifying the specimen submitted and if there are any questions or problems with the specimen the proper person can be notified.

8. Please provide the complete name of the institution referring the patient. If different from the treating institution, indicate the investigator, pathologist, and patient's surgical pathology number where the original diagnosis was made only if it is different from the treating institution.

9. Sign and date the form.

10. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Barcos' lab.

Maurice Barcos, M.D., Ph.D.
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, New York 14263-0001
Phone: (716) 845-4443
Fax: (716) 845-8077

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: PATHOLOGY ROUTING FORM

CALGB Form:	C-350
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required slides/blocks and pathology reports. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

[1] Specimen: 1. Tissue Blocks/Slides ☐ Does specimen accompany this form? (1-No, 2-Yes)

If ***no***, specify reason: _____
If ***yes***, complete the remainder of this form.

☐☐ ☐☐ ☐☐☐☐ Date pathology report and blocks/ slides submitted
M D Y

☐☐ Number of pathology reports submitted

☐☐ Number of slides submitted ☐☐ Number of blocks submitted

Treating Institution _____

Responsible Investigator _____

Responsible Pathologist _____

Patient's Surgical Pathology Number _____

Institution where original diagnosis was made _____
(Complete only if different from treating institution)

Referring Investigator _____

Referring Pathologist _____

Patient's Surgical Pathology Number _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Maurice Barcos, M.D., Ph.D.
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, New York 14263-0001
Phone: (716) 845-4443
Fax: (716) 845-8077

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

INSTRUCTIONS FOR CALGB SPECIMEN ROUTING FORM (C-383): WHOLE BLOOD

A. Purpose

To provide identifying information that will accompany the tube/tubes of whole blood.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record the patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Code whether the specimen is being sent with this form. If the specimen is not being sent, be sure to record the reason why it is not being sent.

4. Record the month, day, and 4-digit year that the tube/tubes of plasma is being submitted.

5. Record the number of tubes of whole blood being submitted.

6. Please refer to the protocol section regarding preparation of the whole blood for shipment to Dr. Liu's lab.

7. Code whether the specimen collected is a pretreatment sample, was collected during treatment or was collected at the follow-up visit. Ship each specimen separately (eg. pretreatment specimen versus during treatment specimen versus follow-up specimen, etc.).

8. Fill in the name of the treating institution.

9. Fill in the full name of the responsible investigator.

10. Sign and date the form.

11. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Ed Liu's lab.

Edison Liu, M.D.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, North Carolina 27599-7295
Phone: (919) 966-1352
Fax: (919) 966-3015

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: SPECIMEN ROUTING FORM:
WHOLE BLOOD

CALGB Form:	C-383
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required whole blood specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

[2] Specimen: 2. Whole Blood

[ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***,specify reason: _____

If ***yes***, complete the remainder of this form.

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date whole blood specimens submitted
M D Y

Specimen Collected

[ ][ ] Number of tubes submitted

[ ] 1. Pretreatment
2. During Treatment
3. At follow-up visit
4. At relapse

Treating Institution _____

Responsible Investigator _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Edison Liu, M.D.
University of North Carolina
Medical Oncology Division
CB#7295
Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Phone No. (919)966-1352
Fax No. (919)966-3015

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

INSTRUCTIONS FOR CALGB SPECIMEN ROUTING FORM (C-384): PLASMA

A. Purpose

To provide identifying information that will accompany the tube/tubes of plasma.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record the patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Code whether the specimen is being sent with this form. If the specimen is not being sent, be sure to record the reason why it is not being sent.

4. Record the month, day, and 4-digit year that the tube/tubes of plasma is being submitted.

5. Record the number of tubes of plasma being submitted.

6. Please refer to the protocol section regarding preparation of the plasma for shipment to Dr. Hayes' lab.

7. Code whether the specimen collected is a pretreatment sample, was collected during treatment or was collected at the follow-up visit. Ship each specimen separately (eg. pretreatment specimen versus during treatment specimen versus follow-up specimen, etc.).

8. Fill in the name of the treating institution.

9. Fill in the full name of the responsible investigator.

10. Sign and date the form.

11. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Dan Hayes' lab.

Daniel F. Hayes, M.D.
Dana-Farber Cancer Institute
44 Binney Street
D - 1512
Boston, MA 02115
Phone: (617) 632-3472
Fax: (617) 632-3479

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: SPECIMEN ROUTING FORM
PLASMA

CALGB Form:	C-384
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required plasma specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

[3] Specimen: 3. Plasma

[ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***,specify reason: _____

If ***yes***, complete the remainder of this form.

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date plasma specimens submitted
M D Y

Specimen Collected

[ ][ ] Number of tubes submitted

[ ] 1. Pretreatment
2. During Treatment
3. At follow-up visit
4. At Relapse

Treating Institution _____

Responsible Investigator _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Daniel F. Hayes, M.D.
Dana Farber Cancer Institute
44 Binney Street
D-1512
Boston, MA 02115
Phone No. (617)632-3472
Fax No. (617)632-3479

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

APPENDIX II

Questionnaires

C-377 CALGB Family History of Cancer Questionnaire

CALGB Detailed Family History and Exposure Telephone Interview

The CALGB Detailed Family History and Exposure Telephone Interview has been removed and is included as Appendix 2, 10/1/95 - 9/30/96 Progress Report.

FAMILY HISTORY OF CANCER QUESTIONNAIRE
INSTRUCTIONS FOR CALGB PERSONNEL

A. Purpose - The enclosed survey is part of a recently funded project entitled, "Linkage of Molecular and Epidemiologic Breast Cancer Investigations: A Specialized Registry."

We will be using family history information to select patients for participation in a Registry. The Registry will undertake a systematic collection of tumor specimens, as well as treatment outcome, epidemiologic, and molecular data from breast cancer patients enrolled in clinical trials sponsored by CALGB. Several research hypotheses will be investigated using the Registry, including the role of family history in breast cancer prognosis.

B. Form Specific Instructions

1. Please provide this survey to all patients participating in Protocols _____.

2. We request that the patient complete this questionnaire at the time of treatment with a *RED FELT TIP PEN.*

3. After the questionnaire is complete, return it to the data management representative at your institution.

4. The questionnaires will then be mailed to the CALGB Data Management Center at the following address:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705

5. Please try to ensure that all patients on the Protocol are given this questionnaire.

If the patient cannot complete the questionnaire at the time of treatment, they may take it home, but should bring the questionnaire with them at the next treatment.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

Instructions for Patient

Thank you for taking time to complete this confidential questionnaire.

We will ask you about the occurrence of breast and other cancer in your relatives. All of the information you provide on this questionnaire will be held in the strictest of confidence. Neither your name nor any identifying information will appear in any report of the survey.

Based upon your answers to the family history questions, we may wish to contact you again for further information. There is a place on the questionnaire for you to tell us how to reach you in the future. With your help, we hope to learn more about the causes of breast cancer.

At the end of the questionnaire on pages 10 and 11 are comment pages. Use these pages if you need to more fully explain any of your answers. You will also find a space to describe special feelings or insights that you may have about the causes of breast cancer.

If you have any questions about our study or the questionnaire, please feel free to call us toll free at:

1-800-xxx-xxxx Monday - Friday 9 a.m. - 5 p.m.

If a representative is not immediately available, you may leave a message and we will return your call as soon as possible.

When you finish the questionnaire, place it in the envelope provided, and return it to the nurse when she returns to your room.

Thank you very much for your participation.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

INSTRUCTIONS FOR COMPLETING THIS SURVEY

Please proceed with the remainder of the questionnaire. We will be asking questions which require you to provide information about history of cancer in your close relatives.

Make an "X" through the circle which represents your chosen responses with a *RED FELT TIP PEN.*

Example:

Please answer all questions to the best of your ability.

IMPORTANT:

We are asking you about the occurrence of cancer in your full-blood relatives.

We are not referring to step-children, step-siblings, or other half-relations.

If you are adopted and are not able to provide information on blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

Patient's Name_____ Participating Group_____

Patient Hospital Number_____ Participating Group Protocol No._____

Main Member Institution/Adjunct_____ Participating Group Patient No._____

Today's Date

What is your main language: E-English, S-Spanish, O-Other:

(E) (S) (O)

Do you have a phone? N-No,Y-Yes

(N) (Y)

Can we contact you again? N-No,Y-Yes

(N) (Y)

Can we contact you by phone or mail? N-No,Y-Yes

(N) (Y)

Please give us the names, addresses, and phone numbers of two people who will know where you are at all times:

Name:_____

Address:_____

_____

Telephone Number:(___)_____

Name:_____

Address:_____

_____

Telephone Number:(___)_____

What is your present marital status? N- Never Married, M-Married, W-Widowed, S-Separated, D-Divorced

(N) (M) (W) (S) (D)

Are you adopted? Y-Yes, N-No, D-Don't know

(N) (Y) (D)

If "Yes," please read the following:

If you are adopted and you DO NOT KNOW about the cancer history of your blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

We are asking about history of cancer in your blood relatives.

Do you have any full sisters?

(N) (Y) If yes, please specify how many _____

Do you have any full brothers?

(N) (Y) If yes, please specify how many _____

Do you have any daughters?

(N) (Y) If yes, please specify how many _____

Do you have any sons?

(N) (Y) If yes, please specify how many _____

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

Relative		Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
Example		(X) D U	1	2	3	(X)	5	6	N (X) U	2	2	2	(X)	*Stomach*
1	Mother	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
2	Father	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
3	Sister1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
4	Sister2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
5	Sister3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
6	Sister4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
7	Sister5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
8	Sister6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
9	Sister7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
10	Sister8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
11	Sister9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
12	Sister10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
13	Brother1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
14	Brother2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
15	Brother3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
16	Brother4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
17	Brother5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
18	Brother6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
19	Brother7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
20	Brother8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
21	Brother9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
22	Brother10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
23	Daughter1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
24	Daughter2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
25	Daughter3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
26	Daughter4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
27	Daughter5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
28	Daughter6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
29	Daughter7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
30	Daughter8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
31	Daughter9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
32	Daughter10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
33	Son1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
34	Son2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
35	Son3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
36	Son4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
37	Son5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
38	Son6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
39	Son7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
40	Son8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
41	Son9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
42	Son10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

EXTENDED FAMILY

Do you have any other relatives who have been diagnosed with cancer? N-No,Y-Yes

(N) (Y)

If yes please complete the table below:

Relative	Alive or Dead	Type of Cancer
Example: Grandmother	Alive	Ovarian

FAMILY HISTORY QUESTIONNAIRE
COMMENT PAGE

THANK YOU FOR COMPLETING THE FORMAL PART OF OUR QUESTIONNAIRE. BASED UPON YOUR ANSWERS TO THESE QUESTIONS, WE MAY CONTACT YOU IN THE FUTURE. YOU MAY BE ASKED TO PARTICIPATE IN FUTURE STUDIES WHICH ARE AIMED AT INCREASING OUR UNDERSTANDING OF BREAST CANCER. YOUR CONTRIBUTIONS TO THE ON-GOING EFFORT TO UNDERSTAND AND PREVENT BREAST CANCER ARE INVALUABLE TO US.

Please feel free to provide explanations for your answers to any of the preceding questions.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

COMMENT PAGE

Please use this page to write down any special feelings or insights that you may have about breast cancer. We are interested in what you think may have caused your breast cancer.

APPENDIX III

CALGB Policy Governing Genetic Studies

CALGB POLICIES GOVERNING GENETIC STUDIES

Whereas studies of somatic mutations in cancer cells pose little risk to the patient, studies of heritable cancer genes may lead to discrimination by insurers and employers. In addition, the discovery of a familial cancer gene carries with it psycho-social consequences which are only imperfectly understood at present and which add to the above risk. For this reason, all consents for studies of heritable cancer genes must be obtained prospectively. These consents should provide adequate information to allow the patient to assess the risk of participation in the study, and should indicate the steps that CALGB is taking to reduce such risks.

Banked material, already obtained from patients on CALGB protocols may be used for studies of heritable genes, but in this case, a reconsent must be obtained from the patient.

The CALGB will take steps to secure, if possible, a Certificate of Confidentiality from the NIH in order to reduce the risk that disclosure of patient identifiers along with information about gene studies will occur.

CALGB will ask its investigators to advocate the passage of state laws preventing insurers and employers from asking for any information about whether the person has had a diagnosis of cancer or whether the person or family members have been the subject of genetic testing.

Because it is unknown what tests may be appropriate on specimens during the time the specimen is banked, the patient will be asked to grant a broad permission for testing. The patient will be informed that heritable gene studies will be limited to those relevant to cancer. The patient will not be asked to grant permission for each individual laboratory study to be performed. Instead, the patient will be assured that all laboratory investigators will have had their project approved by their respective institutional review board prior to receiving permission to study their tissue.

Access to the tissue bank will be granted upon the recommendation of the appropriate committee overseeing the bank. Each investigator using the bank will provide a written description of the project for which the bank is to be used and will be limited to that project. The investigators must agree that all data resulting from their studies will be furnished to the Data Management Center for entry into the CALGB data base. This agreement will also contain provisions for maintaining patient confidentiality. Clinical information from the CALGB data base will not be provided to users of the bank, except in reports prepared by the CALGB which will lack patient identifiers.

Each protocol describing studies of heritable cancer genes will define optimal patient support and set minimum limits for the level of genetic counseling that must be in place in each institution to allow protocol activation.
The CALGB will establish a committee responsible for review of studies involving heritable cancer genes. The charge to this committee is to consider the short and long-term risks associated with protocols involving studies of heritable genes and to advise the Chair with respect to the appropriate actions concerning these studies. The committee is also responsible for reviewing the resources available for genetic counseling at CALGB member institutions and approving these programs as a requisite for institutional participation in designated protocols. This committee will be comprised of CALGB members as well as representatives of the public.

APPENDIX IV

DHHS Confidentiality Certificate

JUN 24 1996

Karen Sartell, M.A.
Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104

Dear Ms. Sartell:

I am happy to send you the certificate of confidentiality for the research project "Cancer and Leukemia Group B -- Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry."

Please be sure that the informational statement given to participants accurately states the intended uses of personally-identifiable information and the confidentiality protections, including the protection provided by the certificate of confidentiality, with its limitations and exceptions.

May I ask that you advise me of any situation in which the certificate is employed to resist disclosure of information in legal proceedings. I am at 440D Humphrey Building, telephone (202) 690-5896 (direct dial, sometimes answered by machine) or (202) 690-7100, telefax (202) 690-5882. Internet: jfanning@osaspe.dhhs.gov.

If attorneys for the University wish to discuss the use of the certificate, they may contact the Chief Counsel of the Public Health Service, Mr. Richard Riseberg, at (301) 443- 2644.

If you have any questions, or if we can otherwise help, please call.

Sincerely yours,

John P. Fanning
Senior Policy Analyst
Division of Data Policy
Office of Program Systems

CONFIDENTIALITY CERTIFICATE

issued to

Employees of

Cancer and Leukemia Group B
and All Participating Institutions

and Other Participants

conducting research known as

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

In accordance with the provisions of section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)) this certificate is issued to protect the privacy of research subjects by withholding their identities from all persons not connected with the research.

Under authority vested in the Secretary of Health and Human Services under that section, all persons who --

(1) are employed by Cancer and Leukemia Group B, and all participating institutions, and their contractors and cooperating agencies; and

(2) have, in the course of that employment, access to the information which would identify individuals who are the subjects of a research project entitled "Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry"

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research, with the exceptions and limitations set forth below.

The purpose of this research project is to collect breast tissue, plasma and urine from cancer patients; review and confirm the histopathological diagnosis of breast cancer on submitted tissue; gather key family, endocrine and reproductive history, and exposure data, on subjects; and provide specimens to approved investigators for study, and receive results of these studies.

As provided in section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)),

> "Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

The following conditions apply to the protection provided under this certificate:

(1) This certificate does not authorize the Cancer and Leukemia Group B, participating institutions, or their contractors or cooperating agencies to refuse to reveal identifying information concerning research subjects if any of the following conditions exist:

(a) The subject (or, if he or she is legally incompetent, his or her guardian) consents in writing to disclosure of identifying information.

(b) Authorized personnel of the United States Department of Health and Human Services or of the U.S. Army Medical Research and Materiel Command request such information for audit or program evaluation of the research project, or for investigation of the Cancer and Leukemia Group B, participating institutions, or their contractors or employees in carrying out the research project.

(c) Release is required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 301 et seq.) or regulations promulgated thereunder (Title 21, Code of Federal Regulations).

(2) This certificate requires that there be no disclosures of identifying characteristics of research subjects in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to compel disclosure of the identifying characteristics of research subjects, except as provided for in paragraph (1), above.

(3) The confidentiality certificate does not govern the voluntary disclosure of identifying characteristics of research subjects.

(4) This certificate does not represent an endorsement of the research project by the Department of Health and Human Services.

(5) All research subjects in the project will be given a fair, clear explanation of the protection this certificate affords, and of the limitations and exceptions to the protection.

(6) This certificate is effective upon issuance, and will expire at the end of June 2011 or sooner if the holder is notified of cancellation in accordance with the procedures set out in 42 C.F.R. § 2a.8. The protection afforded by this certificate of confidentiality is permanent (including after death) for persons who participated as subjects in the research during any time the certificate was in effect.

Date: JUN 19 1996

Philip R. Lee, M.D.
Assistant Secretary for Health

APPENDIX 2

Telephone Interview

Interviewer ID: _____
Time Interview Began: _____ am/pm
Time Interview Ended: _____ am/pm
Date of Interview: _____
Outcome Code: _____
Reference Date: _____

CALGB DETAILED FAMILY HISTORY AND EPIDEMIOLOGY TELEPHONE INTERVIEW

Hello, my name is _____. May I please speak with (RESPONDENT)? I'm calling from THE LINEBERGER CANCER RESEARCH CENTER AT THE UNIVERSITY OF NORTH CAROLINA CHAPEL HILL. WE ARE CONDUCTING A STUDY ON BEHALF OF CANCER AND LEUKEMIA GROUP B (CALGB).

A. Recently, you indicated your willingness to participate in a study we are conducting of breast cancer patients.
As you recall, we are conducting phone interviews as part of this study. We would like to ask you some questions about your health history. These questions will take about one hour to answer.
Is this a convenient time for you?

(If NO, reschedule.)

If YES:

Thank you very much. Your answers to these questions will help us to understand more about breast cancer. For your future reference here is my name and address:
Name:_____
Lineberger Comprehensive Cancer Center, University of North Carolina
CB# 7500, Chapel Hill, NC 27599
Phone: 1-800-449-0147

B. Your cooperation in the survey is entirely voluntary, and all the information collected will be confidential. Neither your name nor any other identifying information will appear in any report of the survey.

C. The interview will take about 60 minutes. First, I would like to verify some of the previous information you have provided to us.

GO TO SECTION A.

A. VERIFICATION OF PREVIOUS INFORMATION

I. DEMOGRAPHIC INFORMATION

A1. What is your birthdate?

_____mm _____dd _____yyyy

A2. What is the highest degree or year of school you have completed? (DO NOT READ CATEGORIES)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A3. Would you describe yourself as white, black, Hispanic, Asian, or other? (IF OTHER, PROBE FOR ETHNIC GROUP OR RACE)

[ ] WHITE
[ ] BLACK
[ ] HISPANIC OR MEXICAN AMERICAN
[ ] ASIAN OR PACIFIC ISLANDER
[ ] NATIVE AMERICAN
[ ] ALASKAN NATIVE
[ ] OTHER (SPECIFY: _____)

A4. What is your present marital status?

☐ Single
☐ Married
☐ Separated
☐ Divorced
☐ Widowed

A5. IF EVER MARRIED: What is the highest degree or year of school that your husband or partner completed? (DO NOT READ CATEGORIES; IF MORE THAN ONE HUSBAND/PARTNER, ASK FOR MOST RECENT)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (Ph.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A6. In what kind of community do you currently live?

Location	Living now in:
Large city (pop.>100,000)	
Suburb of large city	
Town or city (pop.50,000-100,000)	
Town (pop.<10,000)	
Rural, non-farm (in the country, but not a farm)	
On a farm	

II. FAMILY HISTORY OF CANCER

Now, I would like to review the information that you previously provided to us on the Self-Aministered Family History of Cancer Questionnaire.

First I would like to verify that we are asking about your **FULL BLOOD** Relatives.

A7. **Are you adopted?**

☐ **YES, if yes do you know the health status of your full blood relatives?**
☐Yes, then continue with Family History section. ☐ No, skip to B section and continue questions.

☐ **NO,not adopted, continue with Family History section.**

A8. Now I will be asking about all your full blood relatives and how many you have.

HOW MANY? RELATIVES	NUMBER
SONS	
DAUGHTERS	
BROTHERS	
SISTERS	
PATERNAL AUNTS	
PATERNAL UNCLES	
MATERNAL AUNTS	
MATERNAL UNCLES	

Now, I will be asking about all of your relatives who have been diagnosed **with cancer** and those that have **not** had cancer. **(Names are optional if given and are for identification during interview only.)**

MOTHER'S INFORMATION

A9. Is your mother still living?

[ ] Yes (Name_____)
[ ] No, skip to A11.

A10. How old is your mother? ☐☐☐ , **skip to A12.**

A11. How old was your mother when she died? ☐☐☐

A12. Did your mother ever have breast cancer or ovary cancer?

[ ] YES, BREAST CANCER, ONE BREAST
[ ] YES, BREAST CANCER, BOTH BREASTS
[ ] YES, OVARY CANCER
[ ] NO
[ ] DON'T KNOW OR REMEMBER

A13. How old was she when it was first diagnosed?☐☐☐ (BREAST)
☐☐☐(OVARY)

A14. Did your mother ever have any other kind of cancer?
[ ] Yes
[ ] No, skip to A17

A15. What other kind of cancer(s) did she have?

a. _____

b. _____

A16. How old was she when it was diagnosed?

a. ☐ ☐ ☐

b. ☐ ☐ ☐

FATHER'S INFORMATION

A17. Is your father still living?
[ ] Yes
[ ] No, SKIP TO A19

A18. How old is your father? ☐☐☐ SKIP TO A20

A19. How old was your father when he died? ☐☐☐

A20. Did your father ever have cancer?
[ ] Yes
[ ] No, skip to A23

A21. What kind of cancer(s) did he have?

a. _____

b. _____

c. _____

d. _____

A22. How old was he when it was diagnosed?

a. ☐ ☐ ☐

b. ☐ ☐ ☐

c. ☐ ☐ ☐

d. ☐ ☐ ☐

Let's continue with your sisters and brothers, both living and deceased.

SISTER'S INFORMATION

A23. Altogether, how many FULL sisters have you had? ☐☐ (Number)
[ ] None, or adopted

Sister's Inform.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A. 24 Is your (?) sister still living	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26
A. 25 How old is she?	Age		Age		Age		Age		Age	
A. 26 How old was she when she died?	Age		Age		Age		Age		Age	
A. 27 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A28 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A29 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A30 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A31 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A32 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A33 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

BROTHER'S INFORMATION

A34. Altogether how many FULL brothers have you had? ☐☐

Brothers' Inform.	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A. 35 Is your (?) brother still living	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37
A. 36 How old is he?	Age		Age		Age		Age		Age	
A. 37 How old was he when he died?	Age		Age		Age		Age		Age	
A. 38 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A39 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A40 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A41 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A42 If yes, was he an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

TWIN INFORMATION

A43. Are you a twin?

[ ] Yes
[ ] No, skip to A4?

A44. Which brother or sister is your twin?

[ ] Brother #☐, skip to A46
[ ] Sister #_

A45. Are you identical twins?

[ ] Yes
[ ] No
[ ] Don't Know

MOTHER'S SIDE OF FAMILY

Now I have some questions about other relatives. I will begin with your mother's parents and her side of the family.

A46. First, was your mother adopted?

[ ] Yes, skip to A77
[ ] No
[ ] Don't Know

Mother's Mother (Maternal Grandmother)

A47. Is your mother's mother still living?

[ ] Yes
[ ] No, Skip to A49

A48. How old is your mother's mother? _____Skip to A50

A49. How old was your mother's mother when she died? ___

A50. Did your mother's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A51. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A52. Did your mother's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A53. What kind of cancer(s) did she have?=======**A54.** How old was she when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Mother's Father (Maternal Grandfather)

A55. Is your mother's father still living? [ ] Yes
[ ] No

A56. How old is your mother's father? ____

A57. How old was your mother's father when he died? ____

A58. Did your mother's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A59. What kind of cancer(s) did he have?==**A60.** How old was he when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Now I will ask you about your mother's brothers and sisters, both living and deceased.

Mother's Sisters (Maternal Aunts)

A61. Altogether, how many FULL sisters or did your mother have? ____ (Number)
[ ] None

Mother's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A62 Is her (?) sister still living	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64
A63 How old is she?	Age		Age		Age		Age		Age	
A64 How old was she when she died?	Age		Age		Age		Age		Age	
A65 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A66 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A67 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A68 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A69 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Mother's Brothers (Maternal Uncles)

A70. All together how many full brothers did your mother have? _____(Number)
_____None

Mother's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A71 Is your (?) mother's brother still living	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73
A72 How old is he?	Age		Age		Age		Age		Age	
A73 How old was he when he died?	Age		Age		Age		Age		Age	
A74 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A75 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A76 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I have some questions about your father's parents and his side of the family.

A77. First, was your father adopted?

[ ] Yes, skip to A108
[ ] No
[ ] Don't Know

Father's Mother (Paternal Grandmother)

A78. Is your father's mother still living?

[ ] Yes
[ ] No

A79. How old is your father's mother? ___

A80. How old was your father's mother when she died? ___

A81. Did your father's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A82. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A83. Did your father's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A84. What kind of cancer(s) did she have?

a._____
b._____
c._____

A85. How old was she when it was diagnosed?

a.____
b.____
c.____

Father's Father (Paternal Grandfather)

A86. Is your father's father still living?

[ ] Yes
[ ] No

A87. How old is your father's father? ___

A88. How old was your father's father when he died? ___

A89. Did your father's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A90. What kind of cancer(s) did he have?===**A91**. How old was he when it was diagnosed?

a.________________ a.____
b.________________ b.____
c.________________ c.____

Now I will ask you about your father's brothers and sisters, both living and deceased.

Father's Sisters (Paternal Aunts)

A92. Altogether, how many FULL sisters or did your father have? ____ (Number)
[ ] None

Father's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A93 Is his (?) sister still living	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95
A94 How old is she?	Age		Age		Age		Age		Age	
A95 How old was she when she died?	Age		Age		Age		Age		Age	
A96 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A97 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A98 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A99 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A100 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Father's Brothers (Paternal Uncles)

A101. Altogether, how many FULL brothers did your father have?_____(Number)
[ ] None

Father's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A102 Is your (?) father's brother still living	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104
A103 How old is he?	Age		Age		Age		Age		Age	
A104 How old was he when he died?	Age		Age		Age		Age		Age	
A105 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A106 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A107 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I would like to ask questions about your children. Not adopted children, but your natural children.

Sons

A108. How many sons do you have? Natural sons, not adopted. _____ (Number)

Sons' Inform.	Oldest son		2nd son		3rd son		4th son		5th son	
A109 Is your (?) son still living	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111
A110 How old is he?	Age		Age		Age		Age		Age	
A111 How old was he when he died?	Age		Age		Age		Age		Age	
A112 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A113 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A114 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A115 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A116 If yes, was he an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

Daughters

A117. How many daughters do you have? Natural daughters, not adopted. _____

Daughter's Inform.	Oldest daughter		2nd daughter		3rd daughter		4th daughter		5th daughter	
A118 Is your (?) daughter still living	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120
A119 How old is she?	Age		Age		Age		Age		Age	
A120 How old was she when she died?	Age		Age		Age		Age		Age	
A121 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A122 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A123 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A124 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A125 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A126 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A127 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

COUSINS

A128. Do you have any cousins on your **father's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A129. Which of the following types of cancer have occurred in any of your cousins on your **father's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

A130. Do you have any cousins on your **mother's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A131. Which of the following types of cancer have occurred in any of your cousins on your **mother's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

B. REPRODUCTIVE HISTORY

B1. How old were you when you started having menstrual periods?

- ☐ Less than 12 years of age
- ☐ 12
- ☐ 13
- ☐ 14
- ☐ 15 years of age or older

B2. When did you have your last menstrual period?

- Less than one month ago
- Between one and six months ago
- Six months to one year ago
- More than one year ago

B3. What was your age at your last menstrual period?

Age ___

Subtract current age - above age = ___ - ___ = ___
If difference is five years or greater, skip to question B18.

B4. During the past five years, have you experienced changes in the length of your menstrual period, by this I mean the number of days of bleeding?

- ☐ Yes
- ☐ No

If No, skip to question B7

B5. Describe how the length of your menstrual period has changed in the past five years.

- ☐ Longer duration
- ☐ Shorter duration

B6. How many years ago did this change first occur?

- ☐ Within the past year
- ☐ 1-2 years ago
- ☐ 2-3 years ago
- ☐ 3-4 years ago
- ☐ 4-5 years ago

B7. During the past five years, have you experienced changes in the interval between your menstrual periods?

- ☐ Yes
- ☐ No

If No, skip to question B10

B8. Describe how the interval between your menstrual periods has changed in the past five years:

☐ Longer interval between periods
☐ Shorter interval between periods

B9. How many years ago did this change first occur?

☐ Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B10. During the past five years, have you experienced changes in the amount of bleeding you have with your menstrual cycles?

☐ Yes
☐ No
If No, skip to question B13.

B11. Describe how your periods have changed during this period:

☐ Heavier flow
☐ Lighter flow

B12. How many years ago did this change first occur?
Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B13. During the past five years, have you ever experienced hot flashes or night sweats?

☐ Yes
☐ No
If No, skip to question B16.

B14. How many years ago did this symptom first occur?

☐ Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B15. How often did you experience these symptoms?

____ times per week.
____ times per month.

B16. At present, are you still having menstrual periods?

☐ Yes
☐ No, skip to B18

B17. Please think back to your most recent menstrual period. How many days were there between your most recent period and the period before it? (Count from the first day of one bleeding period to the first day of the next bleeding period).

☐ Exactly ___ days
☐ About ___ days
☐ Do not know

Now skip to B19

B18. Why did you stop having your menstrual periods?

☐Periods stopped naturally

Surgery (check one):
- ☐Hysterectomy (uterus and both ovaries removed)
- ☐Hysterectomy (uterus and one/neither ovary removed)
- ☐Only ovaries removed
- ☐Surgery, but not sure which type

Other Treatments (Check all that apply)
- ☐Chemotherapy
- ☐Radiation therapy

☐Do not know
☐Other (please explain):_____

Now I am going to ask you about your use of hormone replacement therapy>

B19. Have you ever taken estrogen replacement therapy estrogen alone without progestins for conditions related to menopause or menstrual irregularities? **(see color cue card for drug identification and name.)**

☐ Yes
☐ No

B20. How old were you when you first used estrogen for this purpose?

☐☐ Age

B21. At the time you started to take this medication, how often were you having menstrual periods?

☐ Had not had a period for 12 or more months.
☐ Had at least one period in the previous 12 months, but cycles had become irregular.
☐ Periods were fairly regular during the previous 12 months.

B22. For how many years total have you taken estrogen alone for menopause or menstrual irregularities?

☐☐ Years

B23. Have you ever taken oral progestins **(see color cue card)**, either alone or in combination with estrogen, for conditions related to menopause or menstrual irregularities?

☐ Yes
☐ No

B24. How old were you when you first used progestins for this purpose?

☐☐ Age

B25. At the time you started to take this medication, how often were you having menstrual periods?

☐ Had not had a period for 12 or more months.
☐ Had at least one period in the previous 12 months, but cycles had become irregular.
☐ Periods were fairly regular during the previous 12 months.

B26. For how many years total have you taken progestins for menopause or menstrual irregularities?_____(YEARS)

B27. Since your diagnosis of breast cancer have you taken either estrogens or progestins

☐ yes
☐ no, skip to Section C

B28. What type of hormonal preparation have you taken?

☐ estrogen replacement therapy
☐ estrogen and progestin replacement therapy
☐ other _____(specify)
☐ Don't know

B29. Are you taking any of the following medications now?

☐ estrogen replacement therapy
☐ estrogen and progestin replacement therapy
☐ other _____(specify)
☐ Don't know

C. PREGNANCY AND FERTILITY

(Based on section B, if patient has children go to C2.)

Now I am going to ask you questions about your health. First, I would like to ask you about pregnancies you may have had and any medications you may have taken.

C1. Have you ever been pregnant?

☐ Yes
☐ No **(go to C19)**

C2. How many times, in total, have you been pregnant? (This includes live births, stillbirths, miscarriages, and induced abortions.)

Number ☐☐

Now I would like to ask some specific questions about your pregnancies.

C3. What was the result of your (1st, 2nd, etc.) pregnancy? (PROBE: Was it a liveborn, still born, miscarriage or induced abortion?)

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Livebirth				
Stillbirth				
Miscarriage				
Abortion				
Multiple				
Pregnant now				
Don't Know				

C4.How many weeks or months did your pregnancy last?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Full Term				
Early				
Late				
Don't Know				

C5. In what month and year did this pregnancy end?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Month/year				

LIVEBORN ONLY:

C6. Was it a boy or a girl?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Boy				
Girl				
Twin Girls				
Twin Boys				
Twin girl/boy				
other mult.				

LIVEBORN ONLY:

C7. What was the baby's birthweight?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Birthweight Lbs/oz				

C8. Did you breastfeed this(these) child(ren) for 2 weeks or longer?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C9. How long did you breastfeed this (these) child (ren)?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Years				
Still Nursing				

C10. Did you try for 12 months or more to become pregnant for this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C11. Did you take fertility drugs to become pregnant for this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C12. What was the name of the fertility drug?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Medication				
Don't Know (check)				

C13. For how many weeks or months prior to this pregnancy did you take it?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Don't Know				

C14. Did you take medication to prevent miscarriage or "hold" this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C15. What was the name of the medication?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Medication				
Don't Know (check)				

C16. How many weeks pregnant were you when you started taking the medication?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Early				
Late				
Don't Know				

C17. How many weeks or months during this pregnancy did you take it?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Don't Know				

C18. Since your last pregnancy, have you tried for twelve months or more to become pregnant, but were unable to?

[ ] Yes
[ ] No

Now skip to Question C25

C19. Was there ever a time in your life when you tried for at least 12 months to become pregnant without being able to?

[ ] Yes
[ ] No

C20. Have you ever taken fertility drugs, such as Clomid or Perganol, to stimulate ovulation?

[ ] Yes
[ ] No, skip to C27

C21. What was the name of the medication?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Don't Know				

C22. In what month and year did you start taking it?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Month/Year				

C23. For how many months or weeks did you take it?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Months				
Weeks				

C24. Did you take fertility drugs after that? [ ] Yes **(Return to C21 for up to 4 Meds)**
[ ] No

C25. Did you or your husband or partner ever have tests done for fertility?

[ ] Yes
[ ] No, go to C27

C26. Did the doctor say the problem was related to you, your husband or partner, or both of you?

[ ] Self
[ ] Husband/partner
[ ] Both
[ ] No problem
[ ] Doctor didn't know
[ ] Don't know

C27. Have you ever taken birth control pills for any purposes?

[ ] Yes **If "Yes," proceed with questions.**

[ ] No **If "No," please go to C35.**

C.28 For what purpose did you take birth control pills? (Check all that apply.)
[ ] Birth Control
[ ] Regulate menstrual cycles
[ ] other purpose_____

C29. How old were you when you first began taking birth control pills?

☐☐Age

C30. Are you currently taking birth control pills?

☐ Yes ☐ No

C31. Keeping in mind that you may have started and stopped several times, for a **total** of how many years or months did you take birth control pills?

☐ Less than one year
☐ 1 - 3 years total
☐ 4 - 5 years total
☐ 6 - 10 years total
☐ 11 - 15 years total
☐ 16 or more years total

C32. In what month and year did you (first/next) begin to use them?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Month/Year				
Don't Know				

C33. What was the name of the pill you used?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Name				
Don't Know				

C34. How long did you take them continuously this time?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Months				
Years				
Less than 1 mos				
Don't know				

After question C34 skip to C36.

C35. What was the main reason you never used birth control pills?

(CHECK ALL THAT APPLY)
[ ] Doctor recommended against
[ ] Respondent concerned about family history
[ ] Respondent concerned about general safety
[ ] Personal choice, or no need

C36. Are there any other hormone medications that you ever took for any reason, other than those we have already discussed, including **thyroid** medication?

[ ] Yes
[ ] No

C37. What was the name of the medication?

_____
[ ] Don't know

C38. For what reason were you taking this medication?

_____

C39. In what month and year did you start taking it?

__/__

C40. For how many months did you take it? ____

C41. Have you had any pregnancies since you were diagnosed with Breast Cancer?

☐ Yes
☐ No

C42. What was the outcome?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Livebirth				
Stillbirth				
Miscarriage				
Abortion				
Muluple				
Pregnant now				
Don't Know				

D. MEDICAL HISTORY

Now I would like to ask you some more questions about your health.

D1. Did a doctor every tell you that you had any of the following conditions:

CONDITIONS:	YES	AGE WHEN FIRST TOLD OF CONDITION
Gallstones or gallbladder disease		
Endometriosis or Endometrioma		
Diabetes		
Colon polyps (Probe: polyps in the colon		
Uterine fibroids		
Ovarian cyst or cystic ovaries		
High blood pressure (not during pregnancy		
High cholesterol		
Renal Disease or Chronic UTI		
Thyroid Disease		

Now I would like to ask you about some procedures that you may have had in the past. I am going to ask you about procedures prior to your recent diagnosis of breast cancer.

D2. In the past, prior to your recent diagnosis of breast cancer, did a doctor ever tell you that you had fibrocystic breast disease?

[ ] Yes
[ ] No (skip to D4)

D3. How old were you the first time you were told this?

__ __
Age

D4. In the past, prior to any procedures performed as part of your current diagnosis and treatment for breast cancer, did you ever have a breast biopsy or breast aspiration?

[ ] Yes
[ ] No (skip to D8)

D5. What was the reason for the breast biopsy or aspiration?

☐ To follow an abnormal mammogram
☐ To check a lump detected by you
☐ To check a lump detected by your physician

☐ Other_____

D6. In what year was this done?

☐☐☐☐(year)

D7. What was found?

☐ Normal breast tissue
☐ Mastitis
☐ Benign breast disease, including fibrocystic disease
☐ In-situ carcinoma

☐ Other _____

D8. Prior to your diagnosis of breast cancer, did you ever have any surgery that changed the size or shape of your breasts?

[ ] Yes
[ ] No, skip to D11

D9. How old were you when you had this surgery?

__
Age

D10. Which procedure was used? (PROBE)

[ ] PROPHYLACTIC MASTECTOMY
[ ] BIOPSY/LUMPECTOMY
[ ] BREAST PROSTHESIS INSERTED (AUGMENTATION)
[ ] COSMETIC REDUCTION
[ ] OTHER _____

D11. Now I would like to ask you a few questions about your current diagnosis and treatment for breast cancer. In what month and year were you given this most recent diagnosis?

__/__
(month) (year)

D12. Was this cancer diagnosed in your left, right, or both breasts?

[ ] LEFT ONLY
[ ] RIGHT ONLY
[ ] BOTH
[ ] DON'T KNOW

D13. How was this breast cancer discovered: did <u>you</u> first notice a problem, was it found during a routine mammogram, or did you doctor notice a problem?

[ ] SELF-DETECTED
[ ] MAMMOGRAPHY-DETECTED
[ ] PHYSICIAN-DETECTED
[ ] OTHER: _____
[ ] DON'T KNOW

I am now going to ask you some questions about screening mammograms. I would like to know about mammograms performed in the past, before any mammograms performed as part of your recent diagnosis of breast cancer.

D14. Did you have mammograms before the age of forty?

____ Yes, go to D15
____ No, go to D16
____ Don't know, go to D16

D15. How many screening mammograms total did you have prior to age 40?

____ Number
____ Don't know

D16. How often did you have mammograms between the ages of 40 and 50?

☐ More that once per year
☐ Once per year
☐ Once every two years
☐ Less than once every two years
____Never screened
____Not applicable (patient younger than age 40)

D17. How often did you have mammograms between the ages of 50 and 60?

☐ More that once per year
☐ Once per year
☐ Once every two years
☐ Less than once every two years
____Never screened
____ Not applicable (patient younger than age 50)

D18. Is this most recent diagnosis of breast cancer the first time that you have ever had cancer?

[ ] Yes, go to Section E.
[ ] No

D19. Please tell me what type(s) of cancer you have had in the past, including skin and all other cancers, and your age at diagnosis.

Type of Cancer	a	b	c	d
Age at Diagnosis	a	b	c	d

E. SMOKING

E1. Have you smoked at least 100 cigarettes, that is 5 packs or more, in your lifetime?

☐Yes (if yes, go to E2)
☐No (if no, skip to section F)

E2. How old were you when you started smoking cigarettes?

☐☐Age

E3. Do you smoke cigarettes NOW?

☐Yes (if yes, go to E5).
☐No

E4. How old were you when you stopped smoking cigarettes?

☐☐Age

E5. At the PRESENT TIME, on average how many packs of cigarettes do you smoke per day?

☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E6. In the PAST, during the years in which you smoked regularly, on average how many cigarettes did you smoke per day?

☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E7. During the time following your recent diagnosis of breast cancer, on average how many cigarettes have you smoked per day?

☐ None
☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E8. Have you ever smoked a cigar or pipe regularly?

☐Yes (if yes, go to E9)
☐No (if no, go to section F)

E9. How old were you when you started smoking a cigar or pipe?

☐☐Age

E10. How old were you when you stopped smoking a cigar or pipe?

☐☐Age

E11. Do you smoke a cigar or pipe NOW?

- ☐ Yes (if yes, go to E5).
- ☐ No (if no, skip to E6).

E12. Since your recent diagnosis of breast cancer, how often have you smoked a cigar or pipe?

- ☐ Less than once a day
- ☐ Once or twice a day
- ☐ More than twice a day

F. HEIGHT, WEIGHT, PHYSICAL ACTIVITY

Now I have some questions about your weight and level of physical activity in the past ten years.

F1. What has been your lowest weight in the past ten years, not counting this past year?
___lbs
[ ] Don't know

F2. How old were you (during the past ten years) when weighed that amount?
___ yrs old
[ ] Don't know

F3. What is the most that you ever weighed during the past ten years? (PROBE: Do not include any times you were pregnant or nursing.)
___lbs
[ ] Don't know

F4. How old were you (during the past ten years) when you weighed this amount?
___ yrs old
[ ] Don't know

F5. When you gain weight, where on your body do you tend to gain it most easily: below the waist, around and above the waist, or above and below the waist equally? (PROBE: Do not include times when you were pregnant.)

[ ] BELOW THE WAIST
[ ] AROUND AND ABOVE THE WAIST
[ ] ABOVE AND BELOW WAIST EQUALLY
[ ] NEVER CARRIED EXTRA WEIGHT

F6. For the past FIVE years prior to your recent diagnosis of breast cancer, please tell me whether you participated regularly in the following activities: (By "regularly" we mean at least 2 hours per week spent in each activity). **(Check all that apply)**

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

F7. I would like to ask about your participation in these same activities since your recent diagnosis of breast cancer. Since that time, please tell me whether you participated regularly in the following activities: (Again, by "regularly" we mean at least 2 hours per week spent in each activity). **(Check all that apply)**

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

G. ALCOHOL USE

Now I am going to ask you about your consumption of alcoholic beverages.

ALCOHOLIC BEVERAGES include beer, wine and liquor.

G1. In the past five years, have you had at least 12 drinks of any alcoholic beverage?

☐Yes (if yes, go to G2)
☐No (if no, skip to section H)

G2. In the past five years, PRIOR your recent diagnosis of breast cancer, did you consume alcoholic beverages at least once a week?

☐Yes (if yes, go to G3)
☐No (if no, skip to G5)

G3. During this time on how many days did you consume alsoholic beverages in an average week?

_____number
____Don't Know

G4. On the days when you drank alcoholic beverages, how many drinks did you have in a single day, on AVERAGE?

_____number
____Don't Know

G5. Were there any times when you drank more than five drinks of alcohol in a single day?

____yes (go to G6)
____no (go to G7)

G6. In the five years prior to your diagnosis of breast cancer, how many days total did you have more than five drinks in a single day?

_____number
_____Don't Know

Now I am going to ask you about your consumption of alcohol since your recent diagnosis of breast cancer.

G7. Since your recent diagnosis of breast cancer, have you consumed alcoholic beverages at least once a week?

____yes (go to G8)
____no (go to G10)

G8. In an average week, on how many days do you consume alcoholic beverages?
_____number
_____ Don't Know

G9. On the days when you drink alcoholic beverages, how many drinks do you have in a single day on AVERAGE?

_____number
_____Don't Know

G10. Since your recent diagnosis of breast cancer are there any times when you had more than five drinks of alcohol in a single day?

____Yes, Go to G11
____No, Go to section H

G11. Since your recent diagnosis of breast cancer, on how many days have you had more than five drinks of alcohol in a single day?

_____Number
_____Don't Know

H. MEDICATION HISTORY

I am going to ask about some medications you may have taken in the past and may be taking now.

H1. The following table refers to over-the-counter and prescription medications.

In the past five years, PRIOR to your recent diagnosis of breast cancer have you taken any of the following medications on a regular basis? By this we mean three times a week or more for at least one month.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H2. Since your recent diagnosis of breast cancer have you taken any of the following medications on a regular basis? By regular we mean three times a week or more.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H3. Which of the following medications do you take on a regular basis NOW? By regular we mean three times a week or more.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H4. Are there any other medications that you are currently taking for any reason?

☐ Yes
☐ No

H5. Information on medications currently taking, excluding any cancer therapeutic drugs. (Probe: Heart, Kidney, Diabetes, Chronic UTI, Topical steroids, Theophylines, OTC use.)

	First Med	Second Med	Third Med	Fourth Med
Name of med.				
Reason for taking med				
In what month and year did you start taking the med				
For how many months did your take it				

I. VITAMIN SUPPLEMENT HISTORY

NOW I AM GOING TO ASK YOU SOME QUESTIONS ABOUT DIETARY SUPPLEMENTS AND VITAMINS. I WANT TO KNOW IF YOU TOOK OR ARE NOW TAKING THESE SUPPLEMENTS ON A REGULAR BASIS. BY A REGULAR BASIS I MEAN AT LEAST TWO TIMES PER WEEK.

Supplement	**Over the past 5 years, PRIOR to your recent diagnosis of breast cancer, did you take any of the following dietary supplements?**		**Do you take any of the following dietary supplements now?**	
Vitamin A	Yes	No	Yes	No
Vitamin C	Yes	No	Yes	No
Vitamin E	Yes	No	Yes	No
Beta-carotene	Yes	No	Yes	No
Selenium	Yes	No	Yes	No
Iron	Yes	No	Yes	No
Calcium or dolomite	Yes	No	Yes	No
Zinc	Yes	No	Yes	No
Cod Liver Oil	Yes	No	Yes	No
Vitamin B12 or B Complex	Yes	No	Yes	No
Folate or Folic Acid	Yes	No	Yes	No
Multivitamin or Multivitamin with Iron	Yes	No	Yes	No

J. DIETARY HISTORY

J1. Over the past five (5) years, prior to your recent diagnosis of breast cancer, how often did you eat the following types of foods? (Place "X" in the appropriate boxes.)

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

J2. How often do you eat these foods now?

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

J3. Do you currently follow a **vegetarian** diet?
This means you do not consume beef, pork, lamb, poultry or fish.

☐ Yes
☐ No

J4. Over the past five years, did you follow a **vegetarian** diet for a period of one year or more?

☐ Yes
☐ No

K. OCCUPATION AND RESIDENTIAL HISTORY

Those are all my questions about your health and your family. My final questions are about jobs that you may have ever had as an adult and where you have lived during your lifetime.

K1. Where were you born?

_____State

K2. What kind of community did you spend most of your life when you were:

Location	Less than 18 years old	18-25 years old	Greater than 25 years old
Large city (pop.>100,000			
Suburb of large city			
Town or city (pop.50,000-100,000)			
Town (pop.<10,000)			
Rural, non-farm (in the country, but not a farm)			
On a farm			
Don't remember			

K3. Have you ever been employed outside the home?

1[ ] Yes
2[ ] No

K4. When you were employed outside the home, what was the occupation you held for the LONGEST PERIOD OF TIME? (PROBE: What was your complete job title?)

_____(TITLE)

K5. At what age did you start working at this job?_____AGE_____

K6. How many years total did you work at this job?_____ (years)

K7. What was the occupation that you held FOR THE SECOND LONGEST PERIOD OF TIME?_____ (TITLE)

K8. At what age did you start working at this job?_____(AGE)

K9. How many years total did you work at this job?_____(YEARS)

K10. What was the occupation that you held FOR THE THIRD LONGEST PERIOD OF TIME?_____ (TITLE)

K11. At what age did you start working at this job?_____(AGE)

K12. How many years total did you work at this job?._____(years)

K13. IN ADDITION TO THE INFORMATION YOU HAVE PROVIDED, have you worked in the following professions?

OCCUPATION	yes/no	how many years	age at start
Radiology Technician			
Dental Technician			
Veterinary Technician			
Veterinarian			
Medical Doctor			
Dentist			
Laboratory Worker			
Nurse			
Beautician/Hairdresser			
Airline Stewardess			
Managerial/Clerical Worker			

K14. Have you ever worked night shifts in any of your job positions?

☐ Yes
☐ No

How many years total? _____

K15. Have your ever lived or worked on a farm?

☐ Yes
☐ No

How many years total did you live or work on farm? _____

K16. Did you ever mix or apply pesticides or herbicides as part of your job?

☐ Yes
☐ No

K17. Did you ever use pesticides or herbicides in your private garden?

☐ Yes
☐ No

K18. Did you ever use pesticides inside your home? This includes control of roaches, ants, termites, etc.

☐ Yes
☐ No

K19. Did your ever use pesticides on your pets or livestock? This includes flea and tick control products?

☐ Yes
☐ No

K20. Where was this phone interview conducted?

☐ Home
☐ Office
☐ Relative's House
_____ Relative
☐ Other
_____ Where?

K21. Before we end the interview, do you have any comments about the interview or is there anything you would like to add that was not covered by the interview?

_____
_____
_____
_____

K22. Do you have any opinions as to what caused or influenced your breast cancer occurrence? Please feel free to give you feelings about this matter? (Refer to comments from self-administered questionnaire.)

_____
_____
_____
_____

L. END OF INTERVIEW

L1. Thank you very much for your help in our survey. Your answers will be very helpful in our research. May we contact you again if we need additional information?

[ ] Yes
[ ] No, skip to M1.

L2. Could you provide me with the name, address, and phone number of someone who will always know where to get in touch with you?

_____ NAME
_____ ADDRESS
_____
_____ PHONE

L3. With your permission we would like to send you another questionnaire concerning your personal well-being.

[ ] Yes
[ ] No
[ ] Undecided or will let us know

L4. We would like to have your address to mail the questionnaire:

_____ NAME
_____ ADDRESS
_____
_____ PHONE

We will mail you the questionnaire with instructions and will contact you by phone to arrange for a convenient time to obtain your responses.

L5. Thank you again.

END CALL AND RECORD RESULT CODE AND TIME ENDED ON QUESTIONNAIRE COVER

M. INTERVIEWER REMARKS

M1. Were other people present in the room with the patient during the interview?

- ☐ Yes, the whole time
- ☐ Yes, for part of the time
- ☐ No

M2. Respondent's cooperation was:

- ☐ Very Good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Other (Specify)_____

M3. The quality of the responses was:

- ☐ High quality
- ☐ Generally reliable
- ☐ Questionable
- ☐ Unsatisfactory
- ☐ Other (Specify)_____

M4. The respondent:

- ☐ Recalled all information
- ☐ Had trouble with amounts or frequencies
- ☐ Had trouble with dates
- ☐ Had trouble recalling overall
- ☐ Other (Specify)_____

M5. If respondent had difficulty recalling, the reasons for unsatisfactory or questionable information is indicated below:

- ☐ Did not want to be more specific
- ☐ Did not understand or speak English well
- ☐ Was bored or uninterested
- ☐ Was upset, depressed or angry
- ☐ Had poor hearing or speech
- ☐ Was confused or distracted by frequent interruptions
- ☐ Was inhibited by others around her
- ☐ Was embarrassed by the subject matter
- ☐ Was emotionally unstable
- ☐ Was physically ill
- ☐ Became tired and began to not answer or understand as well as early on due to length of questionnaire
- ☐ Other (Specify)

_____

_____

_____

APPENDIX 3

Letters of Agreement for Registry Users

A. First Letter
B. Application
C. Letter of Approval of Project

Appendix 3.A

Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

Dear _____

Thank you for your inquiry about the CALGB "Linked Registry" This registry incorporates information concerning the staging, treatment and outcome of women treated on CALGB breast cancer protocols and couples this with information concerning risk and prognostic factors. In addition, paraffin embedded tumor tissue, DNA from peripheral blood cells, plasma and urine are available on these patients. This registry is supported by a contract with the U.S. Army Research and Materiel Command and is intended to assist a wide variety of investigations into the causes, prevention, and treatment of breast cancer.

The priorities for the use of the registry are established by the Linked Registry Steering Committee. The Steering Committee current membership is as follows:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	P.I.	Central Office
Robert Millikan, DVM, Ph.D	co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Larry Norton, M.D.	Br. Com. Chm	MSKF
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS
Lynne Dressler, M.A.	Linked Registry	U. North Carolina
Debra Collyar	Patient Advocate	External Member
Susan Moore	Patient Advocate	External Member

Use of the data from the Linked Registry: All uses of the Linked Registry will be described in formal appendices to CALGB protocols. These appendices will define the objectives, methodology, and statistical assumptions to be used in the investigation. Investigators are encouraged to submit requests to use the registry in the format of an appendix to our protocols. These will be reviewed by the Steering Committee at one of its regularly scheduled meetings. If approved by the Steering Committee, the appendices prepared by CALGB Protocol Editors for circulation to the Group institutions and the investigator will receive written permission for use of the registry resources.

If you are interested in using the linked registry, please submit a letter of intent to the Chair of the CALGB Correlative Sciences Committee for Solid Tumors. This letter should outline the proposed investigation and the resources required.

members of the Steering Committee. In this way, investigators can be better informed about the current status of the registry and receive input with respect to the feasibility of their request. The Committee Chair will ask those submitting letters of intent consistent with the resources and goals of the registry to prepare a formal application (see below). In addition, the investigators will be invited to describe their projects to those attending the meetings of relevant CALGB Committees which may choose to endorse the proposal and to suggest how it may best proceed within the structure of CALGB.

We point out that users of the registry must agree to follow procedures put in place to protect the privacy of CALGB patients, to insure that CALGB policies concerning data flow and analysis are followed, that responsibility for various tasks related to the project is clearly identified, and that there is agreement with respect to how, where, and by whom the results of the investigation will be reported. These policies and procedures are summarized below. Investigators whose projects have been approved by the Steering Committee must sign a letter in which they agree these provisions before the resources of the registry can be made available to them.

Review of Proposals: Proposals from the scientific community for use of the Linked Registry will be considered if they do not compete with approved projects already underway, and will be prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we will use the same scale that will be used for projects developed by CALGB members. In all cases emphasis will be placed upon the level of innovation and the track-record of the applicant with respect to peer review and publications. We will deliberately include projects, however, from promising young investigators, if they are endorsed by knowledgeable mentors and are innovative. The Steering Committee will use an integrated approach to systematically evaluate scientific hypotheses, which implies that projects will be evaluated for their contribution to ongoing avenues of research.

The Steering Committee will evaluate the proposed methods of quality assurance proposed for use during the investigation. Users of the Registry should be aware that peer review of the CALGB has focused on documentation of methods CALGB uses for quality assurance purposes in this type of research.

Again, thank you for your interest. If what you have learned about the registry so far suggests that it would be helpful to you in your research, we look forward to hearing from you.

Sincerely yours,

O. Ross McIntyre, M.D.
Principal Investigator, CALGB Linked Registry.

Enclosure:

APPENDIX 3.B

APPLICATION FOR USE OF CALGB "LINKED REGISTRY" FOR BREAST CANCER RESEARCH

Date:
Name:
Address:
Institution:
Position/Department

Title of Project:

Hypothesis: [50 words or less]

Attach the following to your application:

Background: [250 words or less]

Specific Aims: [list no more than three. 100 word limit]

Methods: [Provide general description of methods with particular attention to what resources you need from the linked registry. Include description of number and type of samples. Justify with a statistical section. Discuss your plan with CALGB statistician and Chair of the CALGB Committee for Correlative Sciences in Solid Tumors prior to writing this section. Specify the analyses that will be performed using clinical, epidemiologic or other resources from the registry. Two page limit]

Significance: [250 words or less]

Attach Biosketch or CV. Indicate active peer reviewed grants that will be supporting this work or other support for this work. The Linked Registry has no funds to support individual projects.

Policies governing the use of the Linked Registry: The following text will be included in a letter which CALGB will furnish to the investigator who must sign and return it prior to activation of the project:

"This is a collaborative project between you and the Cancer and Leukemia Group B (CALGB). The usual ground-rules for collaborations of this type will prevail. Data from all laboratory tests performed on samples from the registry will be submitted by you to the CALGB Data Management Center. In the usual situation transfer of this data will be via electronic means. At the Data Management Center it will be entered into the CALGB Database for analyses specified in the research plan. These analyses will be conducted by the relevant

CALGB statistician. You agree that all analyses reported from your project will be based upon data contained in the CALGB Database.

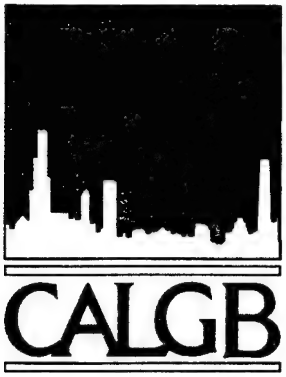
Tissues and other samples are furnished to you by the Linked Registry for the purpose of the project as approved by the Steering Committee. You agree to limit your research to that described in your application unless written approval to change the scope of your investigation is obtained from the Steering Committee. You also agree that you will not furnish materials from the Linked Registry to other parties for any purpose without the written approval of the Steering Committee.

As the lead investigator, it is expected that your name will be listed as the first or last author of publications coming from this project. Other members of your research team may be granted authorship, as appropriate. CALGB personnel, usually the CALGB statistician assigned to this project, relevant members of the steering committee who are responsible for the resource used in the investigation, and others making significant intellectual contributions, will be included as authors. You will acknowledge the support of the Linked Registry Contract from the Army along with the disclaimer " Opinions, interpretations, conclusions, and recommendations expressed in this publication are those of the authors and not necessarily endorsed by the U.S. Army". You will provide the CALGB Central Office with draft copies of manuscripts 30 days prior to submission and abstracts at least 5 days prior to submission, for comment by the CALGB.

If you are not a member of CALGB but are based within a CALGB institution, you may ask that the CALGB Principal Investigator at your institution enter you on our roster. In this way you will be provided with information concerning Group activities that may bear on your project. If you are not at a CALGB institution we will enter your name in the CALGB roster as a " colleague" and ask you to choose a CALGB member as a co-investigator. If you need help in this task, please discuss this with the Chair of the Correlative Sciences Committee for Solid Tumors. The co-investigator will assist with trouble shooting problems within CALGB that may arise during the course of your investigation and will provide other assistance. Ordinarily, the co investigator will also be an author on publications.

The Steering Committee in carrying out its responsibilities for the operation of the Registry will from time to time monitor all projects using the resource. The productivity of ongoing projects and adherence to scientific and ethical standards set by the CALGB will be assessed in this review.

Please submit your proposal in the above format to
CALGB Central Office
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104



Cancer and Leukemia Group B
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208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

Appendix 3.C

Dear _____

I am pleased to inform you that your research plan has been reviewed and approved by the Steering Committee for the CALGB Linked Registry. The Protocol Editor assigned to this study is _____. He/She will be contacting you with respect to any final editing necessary to put the appendix into final form for submission to CALGB institutions. In order for this protocol to be activated we must ask that you sign and date the both copies of this letter. Keep one for your files and return the other to the your protocol editor.

We apologize for the formality of this procedure, but we have found that written understandings of what collaboration has been agreed to is in the interest of both parties. The following text describes the nature of this collaboration :

"This is a collaborative project between you and the Cancer and Leukemia Group B (CALGB). The usual ground-rules for collaborations of this type will prevail. Data from all laboratory tests performed on samples from the registry will be submitted by you to the CALGB Data Management Center. In the usual situation, transfer of this data will be via electronic means. At the Data Management Center it will be entered into the CALGB Database for analyses specified in the research plan. These analyses will be conducted by the relevant CALGB statistician. You agree that all analyses reported from your project will be based upon data contained in the CALGB Database.

Tissues and other samples are furnished to you by the Linked Registry for the purpose of the project as approved by the Steering Committee. You agree to limit your research to that described in your application unless written approval to change the scope of your investigation is obtained from the Steering Committee. You also agree that you will not furnish materials from the Linked Registry to other parties for any purpose without the written approval of the Steering Committee.

As the lead investigator, it is expected that your name will be listed as the first or last author of publications coming from this project. Other members of your research team may be granted authorship, as appropriate. CALGB personnel, usually the CALGB statistician assigned to this project, relevant members of the steering committee who are responsible for the resource used in the investigation, and others making significant intellectual contributions, will be

included as authors. You will acknowledge the support of the Linked Registry Contract from the Army. You will provide the CALGB Central Office with draft copies of manuscripts 30 days prior to submission and abstracts at least 5 days prior to submission, for comment by the CALGB.

If you are not a member of CALGB but are based within a CALGB institution, you may ask that the CALGB Principal Investigator at your institution enter you on our roster. In this way you will be provided with information concerning Group activities that may bear on your project. If you are not at a CALGB institution we will enter your name in the CALGB roster as a " colleague" and ask you to choose a CALGB member as a co-investigator. If you need help in this task, please discuss this with the Chair of the Correlative Sciences Committee for Solid Tumors. The co-investigator will assist with trouble shooting problems within CALGB that may arise during the course of your investigation and will provide other assistance. Ordinarily, the co investigator will also be an author on publications.

The Steering Committee in carrying out its responsibilities for the operation of the Registry will from time to time monitor all projects using the resource. The productivity of ongoing projects and adherence to scientific and ethical standards set by the CALGB will be assessed in this review. You agree to abide by the decisions of the Steering Committee that may come from this review.

Thank you very much and good luck with your investigation.

Sincerely yours,

O. Ross McIntyre, M.D.
Principal Investigator, Linked Registry Project

I agree to the terms of this collaboration.

Signed

_____ Date_____
name

APPENDIX 4

Agenda
Genetics Workshop, November, 1995

GENETIC COUNSELING TRAINING PROGRAM

Saturday, November 4, 1995
6:30 pm to 9:30 pm

Judy Garber, M.D.
Funmi Olopadi, M.D.
Consuelo Skosey, R.N.

I. Breast Cancer Genetics and Prospective

Funmi Olopadi, M.D., Assistant Professor of Medicine, University of Chicago

II. Genetic Cancer Risk Counseling: Ethnic and Cultural Issues

Generosa Grana, M.D., Assistant Professor of Medicine UM.D. NJ, Robert Wood Johnson Medical School

III. Ethical Issues

Judy Garber, M.D., Assistant Professor of Medicine, Dana-Farber Cancer Institute

IV. CALGB 9484: Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry

O. Ross McIntyre, M.D., Professor of Medicine, Dartmouth-Hitchcock Medical Center

APPENDIX 5

Agenda
Genetics Workshop, May, 1996

GENETICS EDUCATION WORKSHOP

Friday, May 3, 1996
7:30 a.m. - 3:00 p.m.

Olufunmilayo Olopade, M.D.

7:30 Continental breakfast

8:00 Welcome - Olufunmilayo (Funmi) Olopade, M.D.

8:15 Introduction to Molecular Genetics

1. Basic Concepts
2. Patterns of Inheritance
3. Past, Current, & Future Endeavors of the Human Genome Project

Shelly Cummings, M.S., Cancer Genetics Counselor, University of Chicago, Department of Hematology/Oncology

9:15 Predictive Testing for Cancer

Funmi Olopade, M.D., Director of Cancer Risk Clinic, Assistant Professor, University of Chicago, Department of Hematology/Oncology

10:00 Obstacles to Testing

Genny Grana, M.D., Robert Wood Johnson Medical School, Assistant Professor of Medicine

10:45 Break

11:00 Psychological Aspects of Predisposition Testing

Andrea Patenaud, M.D., Assistant Professor, Dana-Farber Cancer Institute

11:45 Lunch

1:00 Estimating the Clinical Validity and Utility of Predictive Genetic Tests: Recommendations of the Task Force on Genetic Testing

Neil Holtzman, M.D., Johns Hopkins Medical Institutions

1:45 Role Playing Focused Around the Informed Consent Process/Videotape

Judy Garber, M.D., Assistant Professor of Medicine, Dana-Farber Cancer Institute

2:15 Question & Answer Session

Discussion of CALGB Protocol 9484

Panel of Speakers

APPENDIX 6

Tissue Banking Policy for Paraffin Blocks
in the Linked Tumor Registry

Appendix 6

TISSUE BANKING POLICY FOR PARAFFIN BLOCKS IN THE LINKED TUMOR REGISTRY:

General Policy:

1. All precautions are taken to prevent exhausting tissue on the block.
2. A minimum of three H & E sections (obtained at different thicknesses) will remain on file at the CALGB Pathology office and are available to the submitting institution if needed.
3. A minimum of 2 unstained sections will remain on file and will be available to the submitting institution if needed.
4. Whenever there is an immediate medical or legal need, the unused tissue, along with an H & E section will be returned by overnight mail to the submitting institution.

Standard Tissue Processing:

It is optimal to obtain and bank the entire tissue block so that tissue can be sectioned freshly as needed, as certain antigens (e.g. p53) and other components deteriorate over time when tissue is pre-cut and stored as thin sections. Since it is impossible to predict the effect that extended storage might have on the detection of future markers, a consensus was reached at a recent NCI Inter group Tissue Banking meeting, that tissues be ideally sectioned freshly as needed for biologic makers. Blocks that are submitted to the CALGB pathology office are maintained in a secure space and appropriately recorded into our database. The CALGB is expending significant resources to establish and maintain a tissue surveillance database, expand physical storage capacity and optimize storage conditions for optimal monitoring and quality control for processing, storage and utilization of these tissues. Utilization of tissues occurs only after the proposed scientific study has received approval from the Steering Committee and Solid Tumor Correlative Science committees. Blocks are sectioned freshly for the appropriate assay and are processed in different ways and with special precautions: e.g.. for immunohistochemical studies, 4micron sections on coated slides are prepared and maintained at 4 degrees or colder (-70 degrees is preferable); for DNA extraction studies, 10 micron sections on uncoated slides are prepared carefully to prevent DNA contamination (stored at 4 degrees) and for flow cytometric studies, 3, 50 micron sections are prepared (stored at 4 degrees), in which tumor rich areas are separated from tumor poor areas.

Expedited Tissue Processing:

Although it is optimal to bank blocks so that tissue can be sectioned freshly as needed, we realize that various situations may preclude institutional block submission for banking purposes (institutional policies, legal requirements, minimal embedded tissue). If , for these reasons, a block cannot be maintained in the CALGB Tissue Bank, we ask you to consider submitting the corresponding block for a period of 2-8 weeks, during which time the CALGB pathology office

will expedite tissue processing according to the above guidelines, store the sections at 4 degrees or colder (-70 degrees is preferable) for utilization in companion trials (that do not incorporate labile antigens) and return the blocks to your laboratory.

Institutional Tissue Processing:

Because this material is of great importance for the conduct of CALGB Correlative Science studies and the future direction of our treatment protocols, we would also ask those institutions whose policies prohibit the release of any block from their institution to consider cutting the sections at their own institution. A detailed procedure for sectioning of the specimens can be sent to your laboratory. If needed, we will cover the cost of shipment of the cut sections to the CALGB pathology office. However, as detailed above, sectioning requires special dedication and precautions to prevent cross-contamination from a histotechnician and you may want to reconsider release of the block(s) for a 5 day turn around during which we will expedite the tissue sectioning from these cases.

APPENDIX 7

Pathology Quality Control,
Quality Assurance, and Avoidance of Depletion

APPENDIX 7

PATHOLOGY QUALITY CONTROL AND QUALITY ASSURANCE

Procedure for Cutting Sections for the Linked Registry:

I. Quality assurance:

A. Histotech should wear gloves to prevent DNA contamination

B. Disposable blade should be changed between each block
or
Wipe down blade with 10% bleach, followed by 70% alcohol between each block

C. Clean water bath surface between each block to prevent contamination

D. Clean forceps or other instruments used for separating ribbon between each block

E. All 10 micron sections should be placed on uncoated slides and stored at room temp.

F. All 4 micron sections should be placed on superfrost+ coated slides *

1. H & E sections should be stored at room temperature

2. All other 4 microns sections should be stored in a slide box at 4 degrees.

G. Do not place any cut sections on the slide warmer tray.

II. Sequence of sectioning:

Overall:

top H & E section-coated slide

20, 4 micron sections-coated slide (IHC)

middle H & E (a) section- coated slide

10, 10 micron sections-uncoated slides (Molecular)

middle H & E (b) section - coated slide

3, 50 micron sections- in screw-top glass tubes (Flow Cytometry)

bottom H & E section- coated slide

Labeling:

label all sections with specific pathology block number

label all sections with clinical protocol number and patient protocol

number; indicate group (ECOG, SWOG, CALGB, etc.)

number serial sections (1-20 for 4 micron; 1-10 for 10 micron)

indicate date that sections were cut: "cut date 00/00/00"

top H & E section: label "top"

middle H & E sections: ;label "middle a"; " middle b"

bottom H & E section: label "bottom"

A. Optimal sequence:

1. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining. (label "top")
2. Cut 20, 4 micron sections on coated slides-place in slide box, store at 4 degrees.
3. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle" a)
4. Cut, 10, 10 micron sections on uncoated slides-place in separate slide box and store at room temperature.
5. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle b")
6. Cut, 3, 50micron sections, place curled sections in a screw top glass tube
7. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "bottom")

B. When minimal tissue is available: omit the 50 micron sections for flow cytometry first, then if there is still insufficient tissue to cut the 20 4micron sections for IHC and 10, 10micron sections for molecular; follow the following procedures (each level indicates less tissue available for cutting):

Level I.: (10, 4u;5,10u)

1. Cut top H & E section (coated slide).
2. Cut 10,4 micron sections (coated slide)
3. Cut middle H & E section (coated slide)
4. Cut 5, 10 micron sections (uncoated slide)
5. Cut bottom H & E section (coated slide)

Level II:(5,4u; 3, 10u)

1. Cut top H & E section (coated slide)
2. Cut 5,4 micron sections (coated slide)
3. Cut middle H & E section (coated slide)
4. Cut 3, 10 micron sections (uncoated slide)
5. Cut bottom H & E (coated slide)

Level III: (10 ,4 u sections; 5 on coated slides, 5 on uncoated slides)

1. Cut top H & E section (coated slide)
2. Cut 5, 4micron sections (coated slide)
3. Cut 5, 4 micron sections (uncoated slides)
4. Cut bottom H & E section (coated slide)

Note: 5 sections on uncoated slides; no middle H & E needed.

APPENDIX 8

Letter of Support from Dr. Schilsky

Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

October 25, 1996

Mr. Jimmy Connors
Director, U.S. Army Medical Research
Acquisition Activity
ATTN: SGRD-RMA-RM
Fort Detrick
Frederick, MD 21072-5014

Re: DAMD17-94-J-4114

Dear Mr. Connors:

As the Group Chairman of the CALGB, I enthusiastically support the project, "Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry."

This is an important study and one that I am strong encouraging participation in by CALGB investigators. The enclosed protocol has been extensively revised and the changes made should facilitate activation of the study at most CALGB institutions leading to more rapid accrual in the coming year.

Sincerely,

Richard L. Schilsky, M.D.
Group Chairman, CALGB